# BACKGROUND INFORMATION

# FOR

# THE ARTHRITIS ADVISORY COMMITTEE

**12 July 2016**

***BIOLOGICS LICENSE APPLICATION FOR ABP 501***

**Submitted: 09 June 2016**

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## 1. EXECUTIVE SUMMARY

ABP 501 was developed as a biosimilar product to the United States (US)-licensed reference product, Humira® (adalimumab [US]). Adalimumab is approved for use in a number of inflammatory diseases, including arthritides, dermatological conditions, and inflammatory bowel diseases. The primary mechanism of action in all indications of use is adalimumab binding to the soluble form of human tumor necrosis factor alpha (TNF$\alpha$), a cytokine that mediates inflammatory responses. TNF$\alpha$ also exists in a transmembrane form, and binding to this form, subsequent signaling, and immune-mediated mechanisms may be of relevance in inflammatory bowel disease indications.

Amgen followed the Food and Drug Administration (FDA) recommended stepwise approach to establish the similarity of ABP 501 and adalimumab for all approved indications of adalimumab. The totality of evidence, which includes analytical and nonclinical assessments, a pharmacokinetic (PK) similarity study, and clinical studies in 2 sensitive populations, has established that ABP 501 and adalimumab are highly similar, with no clinically meaningful differences in terms of the safety, efficacy, and immunogenicity of the products. The totality of evidence supports the approval of ABP 501 as a biosimilar to adalimumab in each of the proposed indications.

### Analytical Similarity

The ABP 501 analytical similarity assessment was designed based on a comprehensive review of available literature regarding the structural and purity attributes, and functional activities of adalimumab. Additionally, Amgen supplemented the literature findings with characterization studies of adalimumab and knowledge gained from experience in manufacturing monoclonal antibodies. Using this information, a comprehensive analytical similarity plan that included approximately 100 attribute/assay combinations was defined to assess the structural and functional similarity of the products. Amgen conducted a global development program for ABP 501, including the use of adalimumab procured in the US (adalimumab [US]), and in the European Union (adalimumab [EU]) in the comparative clinical studies in patients. As reflected in FDA guidance, this approach is acceptable provided a “scientific bridge” is established between the US reference product and the foreign-sourced comparator. This scientific bridge must show the analytical similarity of the 2 sources of reference product, and also include a demonstration of PK similarity. ABP 501 lots were therefore compared with lots of adalimumab (US), as well as with lots of adalimumab (EU).

Analytical similarity was first assessed with respect to structural and purity attributes, wherein a large majority of the attribute/assay evaluations met the pre-defined assessment criteria. However, as expected for a biosimilar, some minor analytical differences were observed in a small number of structural and purity attributes when comparing ABP 501 and adalimumab. Specifically, glycan mapping showed ABP 501 to have slightly different levels of high mannose, afucosylated species, sialic acid, and galactose as compared to adalimumab. In addition, differences were observed in the basic and acidic peaks by cation exchange HPLC, which were attributed to differences in the levels of C-terminal lysine variants, and the formation of deamidated species. The same deamidated species are present in both products, and the rates of formation of these were similar between the products. Minor differences in glycan occupancy and partially reduced species were also observed as assessed using reduced and non-reduced capillary electrophoresis methods, respectively. Overall, each difference, at the low levels observed, was considered unlikely to affect the safety, efficacy, or immunogenicity of ABP 501, based on the existing knowledge of the clinical relevance of these differences in attributes. Further evidence for the lack of expected effect on efficacy was provided by the comprehensive functional similarity assessment.

To assess the functional similarity of ABP 501 to adalimumab, the testing focused on the primary mechanism of action, ie, binding to and neutralization of soluble TNFα. The assessment also included additional activities, such as binding to transmembrane TNFα, the induction of antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC), and the inhibition of cellular proliferation in a mixed lymphocyte reaction. These additional activities may contribute to efficacy in the inflammatory bowel disease indications. Further, assays intended to provide additional characterization of functional similarity were also performed, including an assessment of kinetics of binding to TNFα, and alternative signaling pathways neutralized by the inhibition of TNFα. The complete list of functional similarity methods is provided in Table 1.

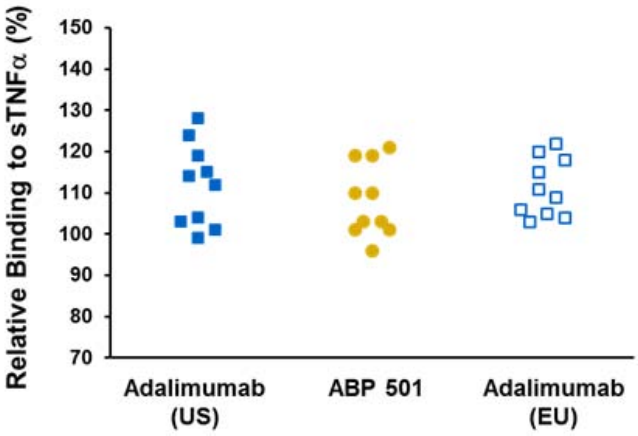
**Table 1. Assays Performed to Assess Functional Similarity**

| Fab-mediated Activities | Fab- and Fc-mediated Activities | Fc-mediated Activities |
|---|---|---|
| Apoptosis inhibition bioassay | Inhibition of proliferation in a mixed lymphocyte reaction | FcγRIIIa (158V) binding |
| Soluble TNFα binding | ADCC | FcγRIIIa (158F) binding |
| Binding kinetics to soluble TNFα | CDC | FcγRIIIa (158V) + TNFα binding |
| Inhibition of soluble TNFα-induced IL-8 in HUVEC | | FcγRIIa (131H) binding |
| Inhibition of soluble TNFα- induced cell death in L929 cells | | FcγRIa binding |
| Inhibition of soluble TNFα-induced chemokines in whole blood | | C1q binding |
| Specificity against LTα in a HUVEC assay | | FcRn binding |
| Binding to transmembrane TNFα | | |

ADCC = antibody-dependent cell-mediated cytotoxicity; C1q = complement component 1,q; Fab = fragment antigen binding; Fc = fragment crystallizable; FcγRIa = Fc-gamma receptor type Ia; FcγRIIa = Fc-gamma receptor type IIa; FcγRIIIa = Fc-gamma receptor type IIIa; FcRn = Fc neonatal receptor; HUVEC = human umbilical vein endothelial cells; LTα = lymphotoxin alpha; TNFα = tumor necrosis factor alpha.

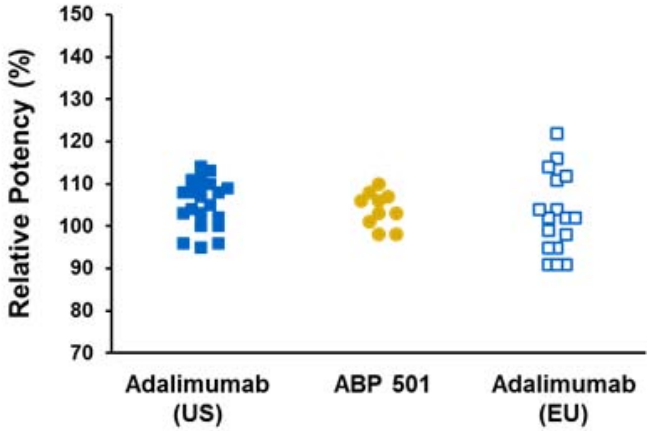
No differences were observed in any of the functional activities assessed, including assays that addressed all of the known, or plausible, mechanisms of action. Therefore, the conclusion that the minor differences observed in the structural comparisons for ABP 501 and adalimumab are unlikely to affect clinical efficacy for ABP 501 was confirmed. Notably, the binding to soluble TNFα (the primary mechanism of action for adalimumab) and the inhibition of apoptosis (a downstream measure of the binding and inhibition of soluble TNFα) were similar between ABP 501 and adalimumab (Figure 1 and Figure 2).

**Figure 1. Relative Binding to Soluble TNFα**




sTNF = soluble tumor necrosis factor alpha.

**Figure 2. Relative Inhibition of Apoptosis**




The results of the analytical similarity assessment established that ABP 501 is highly analytically similar to adalimumab. The functional similarity results also form an essential element of the scientific assessment for extrapolation, ie, the consideration of whether ABP 501 can be expected to perform similarly to adalimumab in all indications, including those that were not specifically studied in ABP 501 clinical trials. Given that functional similarity was demonstrated in all of the activities assessed, including those that are known or suspected to contribute to efficacy in each of adalimumab's approved indications, the functional similarity results provide compelling evidence in support of extrapolation.

**Nonclinical Toxicology**

A nonclinical study in cynomolgus monkeys was performed with the objectives of assessing toxicokinetic similarity and demonstrating qualitatively similar toxicological effects between ABP 501 and adalimumab. ABP 501 and adalimumab had similar toxicokinetics and both induced the expected lymphoid changes in cynomolgus monkeys. Additionally, the toxicities observed were consistent with adalimumab published results. Nonclinical similarity was concluded based on the study results.

**Comparative Clinical Studies**

To confirm the analytical and nonclinical similarity, and to demonstrate clinical similarity with respect to PK, efficacy, safety, and immunogenicity, Amgen designed a clinical development program consisting of the 3 studies shown in Table 2. Amgen selected subject populations and clinical endpoints that would be sensitive to detect any potential clinically meaningful differences between ABP 501 and adalimumab, if such differences

existed. The studied populations were also chosen as being representative of all patient populations in which treatment with adalimumab is approved.

**Table 2. ABP 501 Clinical Studies**

| Study Number | Subject Population | Type of Study | Number of Subjects | Study Duration | Primary Endpoint |
|---|---|---|---|---|---|
| 20110217 | Healthy subjects | PK similarity | 203 | 63 days | $AUC_{inf}$ and $C_{max}$ |
| 20120262 | Rheumatoid arthritis | Efficacy, safety, and immunogenicity | 526 | 26 weeks | ACR20 at week 24 |
| 20130258 (Complete, analysis ongoing) | | Long-term safety and efficacy | 467 | 72 weeks | Safety, DAS28-CRP, ACR20 |
| 20120263 | Plaque psoriasis | Efficacy, safety, and immunogenicity | 350 | 52 weeks | PASI percent improvement from baseline at week 16 |

ACR20 = 20% improvement in American College of Rheumatology core set measurements; $AUC_{inf}$ = area under the concentration time curve at infinite time; $C_{max}$ = maximum observed drug concentration during a dosing interval; DAS28-CRP = Disease Activity Score 28 C-reactive protein; PASI = Psoriasis Area and Severity Index; PK = pharmacokinetic.

Study 20110217 in healthy subjects was designed to assess PK similarity in a study population that does not receive concomitant medications and does not have medical conditions that could potentially affect PK. Healthy subjects are thus considered a sensitive population to detect any potential exposure differences between ABP 501 and adalimumab.

Study 20120262 in subjects with moderately to severely active rheumatoid arthritis (with concomitant methotrexate) was a 26 week study intended to demonstrate that there are no clinically meaningful differences between ABP 501 and adalimumab (US) in terms of safety, efficacy, and immunogenicity. The primary efficacy endpoint of 20% improvement in American College of Rheumatology core set measurements (ACR20) at week 24 is a sensitive endpoint for a comparison of efficacy between ABP 501 and adalimumab. ACR20 has been widely used for the assessment of efficacy in adalimumab rheumatoid arthritis studies, demonstrating a large effect size that is indicative of its ability to detect potential differences in efficacy. Amgen also conducted an open-label extension study for subjects who completed Study 20120262 and chose to continue treatment with ABP 501, which will ultimately provide 2 years of subject exposure.

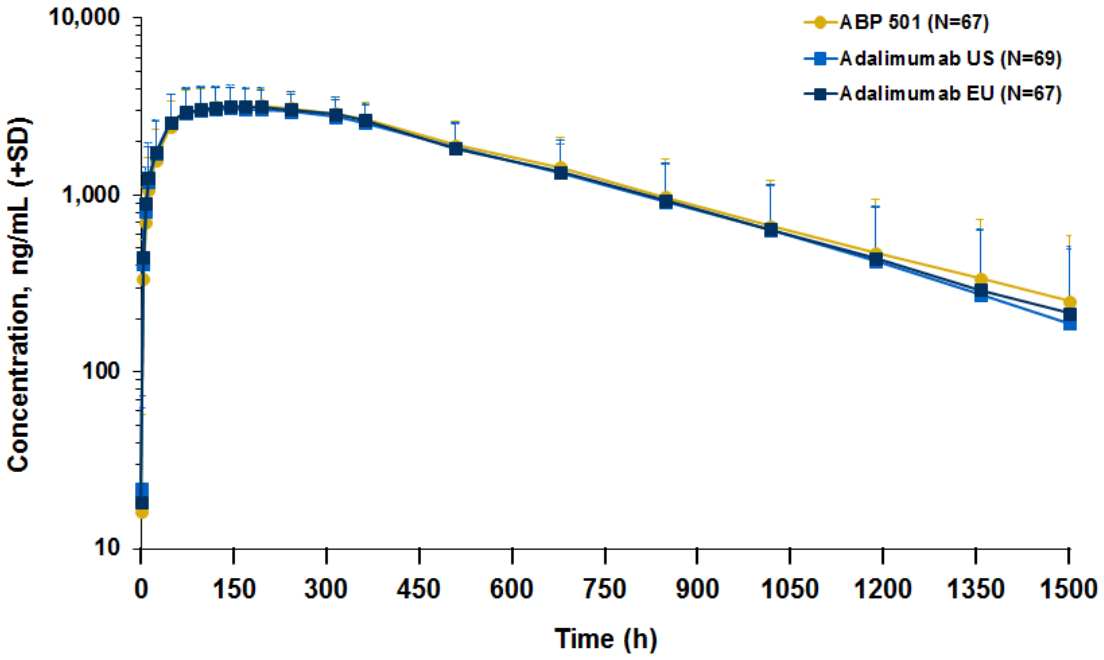
Study 20120263 in subjects with moderate to severe chronic plaque psoriasis (with no systemic immunosuppressants) was a 52 week study intended to demonstrate that there are no clinically meaningful differences between ABP 501 and adalimumab (EU) in terms of safety, efficacy, and immunogenicity. The plaque psoriasis patient population tends to be relatively younger than the rheumatoid arthritis population, with fewer comorbidities and without concomitant immunosuppressive therapy. The primary efficacy endpoint of Psoriasis Area and Severity Index (PASI) percent improvement from baseline at week 16 is a sensitive endpoint for an evaluation of efficacy between ABP 501 and adalimumab and was selected since it is a continuous parameter and is sensitive for the detection of differences in products, if such differences exist. The PASI endpoint has also demonstrated a large treatment effect. Thus, the trial design is considered appropriate for demonstrating no clinically meaningful differences between ABP 501 and adalimumab, with respect to efficacy, safety, and immunogenicity.

Study 20120263 also provides comparative data in a subset of subjects who underwent a single transition from adalimumab to ABP 501 at week 16. Subjects who received adalimumab prior to week 16 and stayed on adalimumab after re-randomization served as a control arm through week 52. The purpose of the comparative analysis was to establish safety, efficacy, and immunogenicity following a single physician-supervised transition from adalimumab to ABP 501.

**Clinical Pharmacology Results**

PK similarity in healthy subjects was assessed between ABP 501 and adalimumab (US), ABP 501 and adalimumab (EU), and adalimumab (US) and adalimumab (EU) following a single 40 mg subcutaneous injection. In accordance with FDA guidance and standards for bioequivalence studies, the 90% confidence intervals of the geometric means ratios for maximum observed concentration ($C_{max}$), and area under the serum concentration-time curve from time 0 to infinity ($AUC_{inf}$) were assessed. Each ratio was determined to be fully contained within the standard bioequivalence margin of 0.80 to 1.25, and thus PK similarity was demonstrated. The serum concentration-time curves are shown in Figure 3.

**Figure 3. Study 20110217 Mean (+SD) Serum Concentration-time Profiles (Pharmacokinetic Parameter Population)**




SD = standard deviation.

The safety profiles were similar across treatment groups. Administration of ABP 501 or adalimumab to healthy subjects resulted in similar rates of both binding and neutralizing anti-drug antibodies.

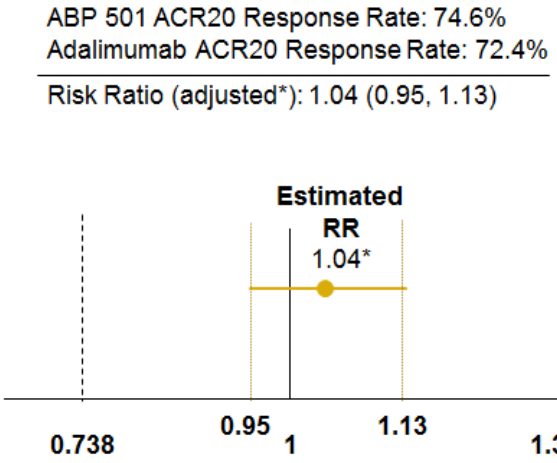
In addition to Study 20110217, trough concentrations of ABP 501 and adalimumab were also assessed in the rheumatoid arthritis and plaque psoriasis studies. The results were highly consistent between the products, also indicating similar exposure of ABP 501 with adalimumab in multiple conditions of use.

### Comparative Clinical Study Results

**Clinical Study in Subjects with Moderately to Severely Active Rheumatoid Arthritis**

At week 24, 74.6% of subjects (194 of 260 subjects) in the ABP 501 group and 72.4% of subjects (189 of 261 subjects) in the adalimumab group met ACR20 response criteria, which is consistent with the adalimumab responses reported in literature. The primary endpoint, risk ratio of ACR20 between ABP 501 and adalimumab, was 1.04 with a 90% confidence interval of (0.95, 1.13), which was well within the pre-defined equivalence margin of (0.738, 1.355). Therefore, clinical equivalence was demonstrated (Figure 4).

**Figure 4. Study 20120262 Primary Endpoint: Risk Ratio of ACR20 at Week 24 (Full Analysis Set, Last Observation Carried Forward)**

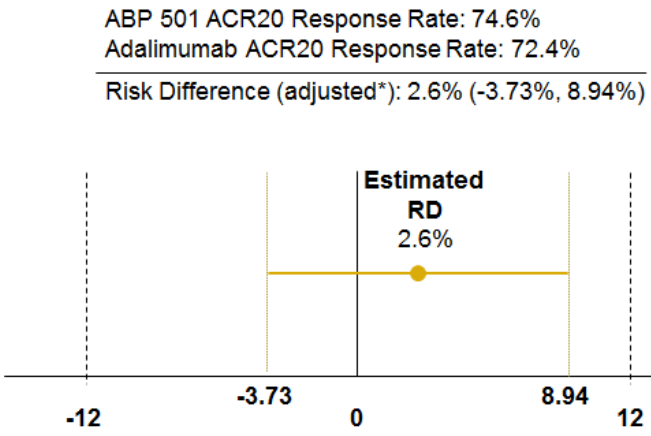



ACR20 = 20% improvement in American College of Rheumatology core set measurements; RR = risk ratio.

*ACR20 Risk ratio and its confidence interval were estimated with a statistical model adjusted for covariates.

FDA recommended that a risk difference of ACR20 with a ± 12% margin should also be considered in the determination of clinical equivalence after the database was locked for the study. The additional analysis showed a risk difference of 2.6% between ABP 501 and adalimumab and a 90% confidence interval of (-3.73, 8.94), which is well within the FDA-recommended margin, confirming the clinical equivalence of ABP 501 and adalimumab (Figure 5).

**Figure 5. Study 20120262 Risk Difference of ACR20 at Week 24 (Full Analysis Set, Last Observation Carried Forward)**




ACR20 = 20% improvement in American College of Rheumatology core set measurements; RD = risk difference.

*ACR20 Risk Difference and its confidence interval were estimated with a statistical model adjusted for covariates.

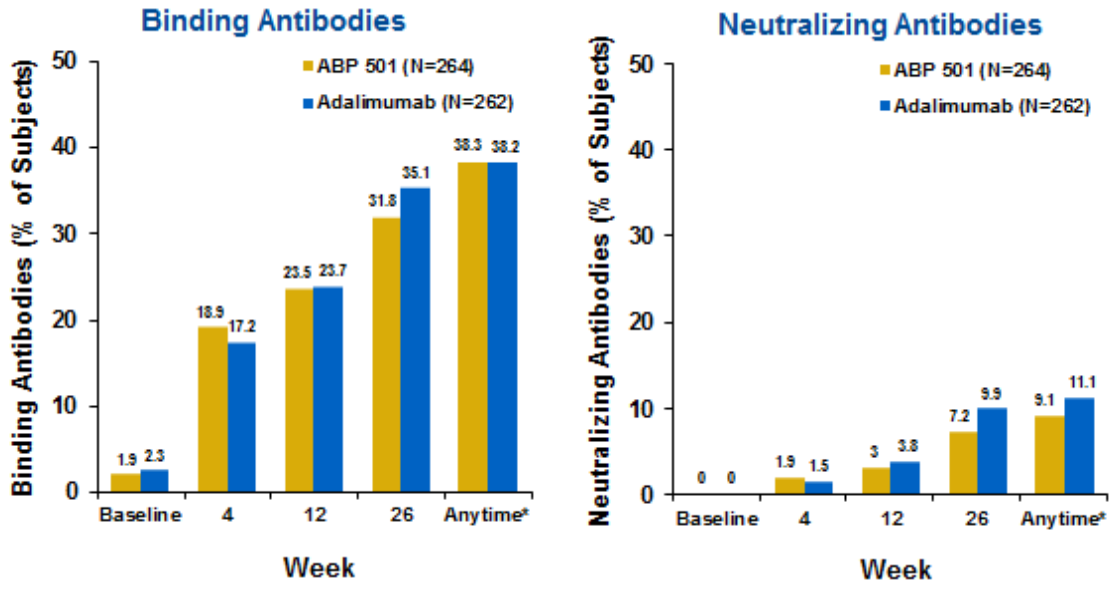
Similar results were observed for all sensitivity analyses, as well as for multiple covariates assessed, thereby confirming the primary efficacy analysis result. The results

for secondary efficacy endpoints also demonstrated similar efficacy between ABP 501 and adalimumab.

No clinically meaningful difference was observed in the safety profiles of ABP 501 and adalimumab in subjects with moderately to severely active rheumatoid arthritis. Overall, 132 (50.0%) subjects on ABP 501 and 143 (54.6%) subjects receiving adalimumab had an adverse event on study, with 10 (3.8%) and 13 (5.0%) subjects having serious adverse events, respectively. The safety profiles were similar across treatment groups and were consistent with the known safety risks of adalimumab.

An immunogenicity comparison of ABP 501 and adalimumab was performed in the rheumatoid arthritis population treated with methotrexate, an immune-modulating drug. The overall summary of the anti-drug antibody incidence rate of subjects developing binding and neutralizing antibodies for ABP 501 and adalimumab is presented in Figure 6. As shown, the binding and neutralizing anti-drug antibody incidence rates were similar between ABP 501 and adalimumab. The observed rates for both products were higher than previously reported for adalimumab (Bloem et al, 2015) because of the use of different methods with improved sensitivity and drug tolerance compared to those used during the original development of adalimumab.

**Figure 6. Study 20120262 Binding and Neutralizing Anti-drug Antibody Results**

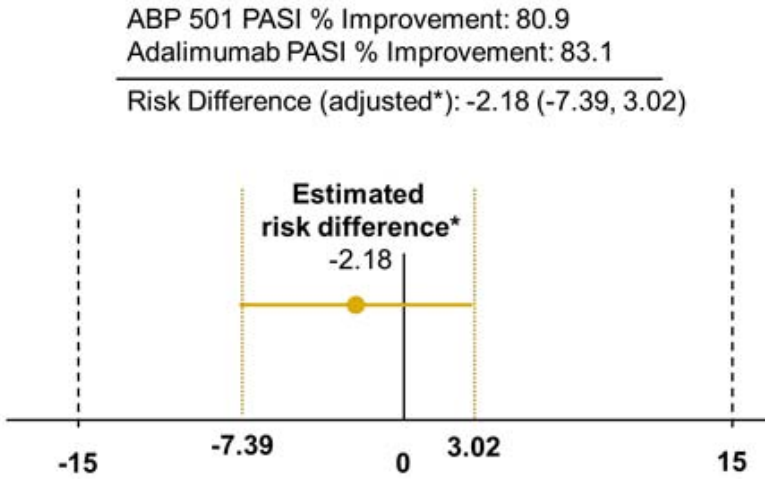



* post-baseline

**Clinical Study in Subjects with Moderate to Severe Chronic Plaque Psoriasis**

Results from the 52 week Study 20120263 confirmed the clinical equivalence of ABP 501 to adalimumab as measured by PASI percent improvement from baseline through week 16, the primary endpoint. The mean (standard deviation) PASI score at baseline was 19.68 (8.10) and 20.48 (7.88) for the ABP 501 and adalimumab treatment groups, respectively. At week 16, the mean (standard deviation) PASI score for the ABP 501 treatment group was 3.74 (5.09), an improvement of 80.91%, compared with 3.29 (5.80), an 83.06% improvement for the adalimumab treatment group. The PASI results are consistent with the adalimumab responses documented in the literature. The treatment difference observed between the 2 groups was -2.18 with a 95% confidence interval of (-7.39, 3.02). The 95% confidence interval was well within the pre-defined equivalence margin of (-15, 15), thus demonstrating equivalence in clinical efficacy between ABP 501 and adalimumab (Figure 7).

**Figure 7. Study 20120263 Primary Endpoint: PASI Percent Improvement at Week 16 (Full Analysis Set, Last Observation Carried Forward)**



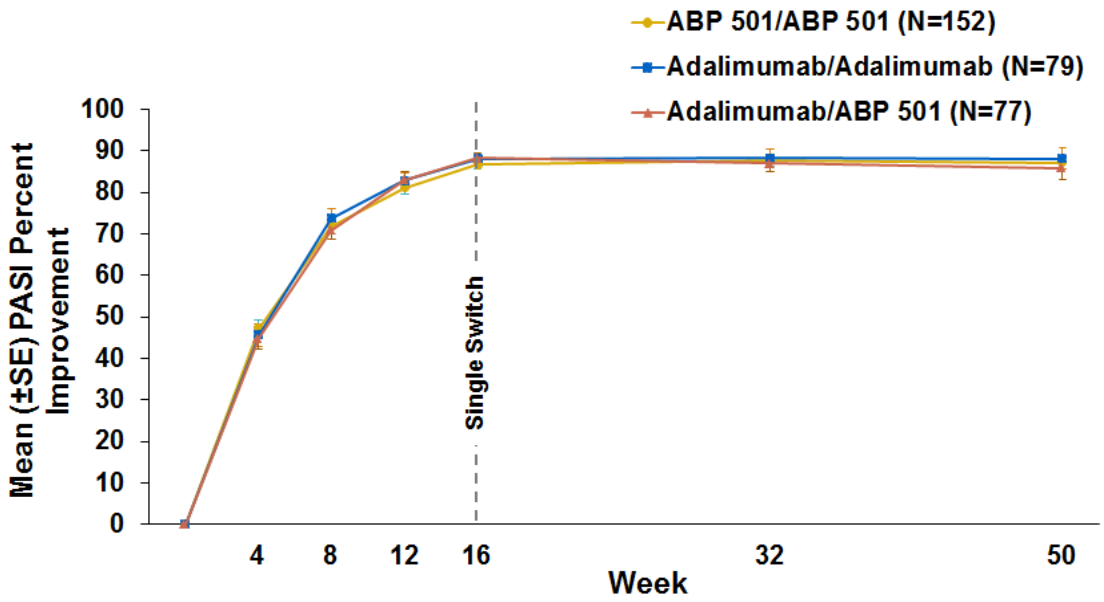

PASI = Psoriasis Area and Severity Index.

*Risk difference and confidence interval were calculated with statistical model adjusted for covariates.

Similar results were observed for all sensitivity analyses, as well as for multiple covariates assessed, confirming the primary efficacy analysis result. The subset of subjects who underwent a single transition from adalimumab to ABP 501 at week 16 and continued up to week 52 also demonstrated similar efficacy compared with subjects who maintained treatment with adalimumab.

The results for the mean PASI percent improvement over time, from baseline through week 52, are shown in Figure 8.

**Figure 8. Study 20120263 Mean PASI Percent Improvement From Baseline Over Time – Through Week 52 (Full Analysis Set, Last Observation Carried Forward)**



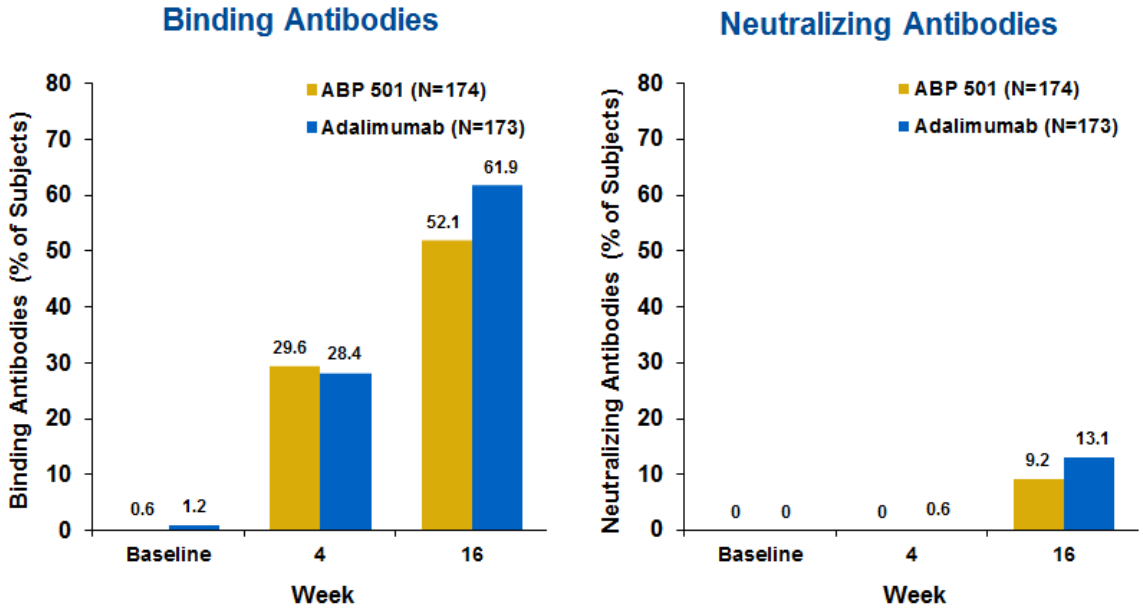

PASI = Psoriasis Area and Severity Index; SE = standard error.

No clinically meaningful difference in the safety profiles of ABP 501 and adalimumab was observed in subjects with moderate to severe chronic plaque psoriasis, including in those patients that underwent a single transition from adalimumab to ABP 501. Following treatment through week 16, there were 117/174 (67.2%) subjects on ABP 501 with an adverse event compared to 110/173 (63.6%) subjects on adalimumab. Serious adverse events were infrequent; 6/174 (3.4%) subjects on ABP 501 had a serious adverse event compared to 5/173 (2.9%) on adalimumab. Following the transition at week 16 and through week 52, there were 108/152 (71.1%) subjects in the ABP 501/ABP 501 arm with an adverse event compared to 52/79 (65.8%) subjects on adalimumab, and 54/77 (70.1%) in subjects that transitioned from adalimumab to ABP 501 (adalimumab/ABP 501 arm). Serious adverse events were also infrequent following transition; 4/152 (2.6%) subjects in the ABP 501/ABP 501 arm had a serious adverse event compared to 4/79 (5.1%) in the adalimumab/adalimumab arm and 4/77 (5.2%) in the adalimumab/ABP 501 arm. The safety profiles were similar across treatment groups and were consistent with the known safety risks of adalimumab.

The incidence of binding or neutralizing antibodies in subjects treated with drug was comparable between ABP 501 and adalimumab through the primary analysis at week 16 and across treatment groups post week 16. As shown in Figure 9, there was an increased incidence of binding and neutralizing antibodies with continued exposure from

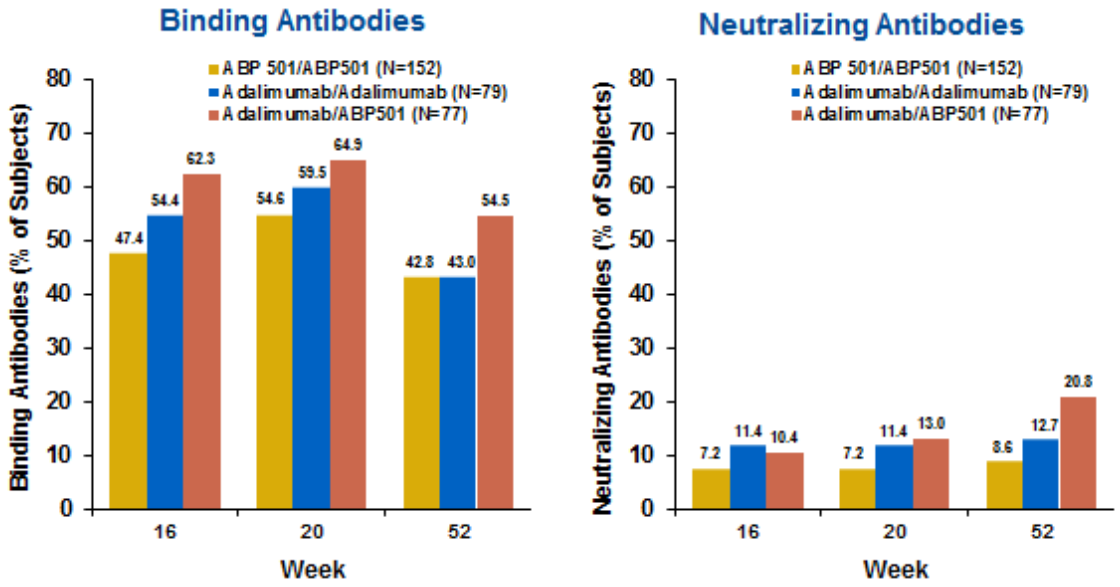
week 4 through week 16. This increasing rate of binding and neutralizing antibody development with exposure is known for adalimumab. The observed incidence rates for anti-drug antibodies were higher than originally described for adalimumab, as was observed in the PK similarity and rheumatoid arthrtitis studies, because of the highly sensitive and drug tolerant assays currently used. However, the importance of the immunogencitiy assessment for biosimilarity is the rates of anti-drug antibodies between the biosimilar and the reference product, and they are similar between ABP 501 and adalimumab.

**Figure 9. Study 20120263 Binding and Neutralizing Anti-drug Antibodies Summary Results Anti-Drug Antibodies Through Week 16**



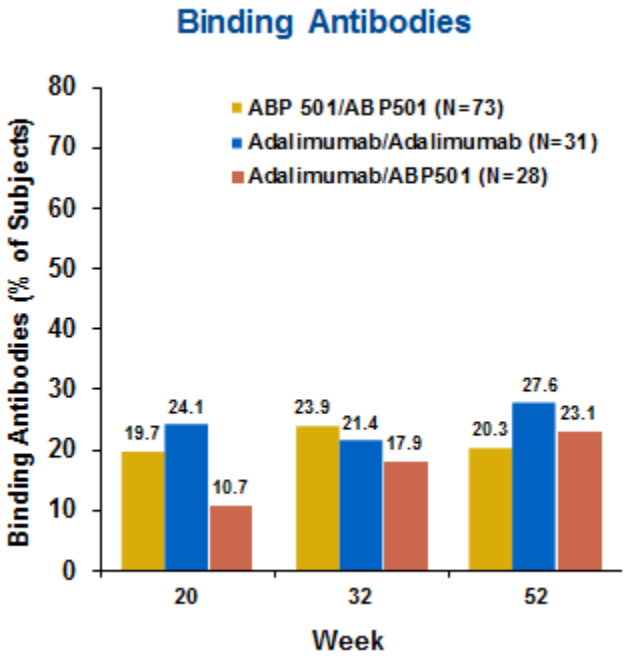

At week 16, subjects in the adalimumab arm were re-randomized to either transition to ABP 501 or continue on adalimumab treatment. This re-randomization led to more subjects with binding anti-drug antibodies in the adalimumab/ABP 501 arm even prior to receiving the first dose after the transition. As shown in Figure 10, the rate of binding antibodies that formed after the transition at week 16 was comparable from week 20 through week 52 between the groups. Subjects with binding antibodies are predisposed to form neutralizing antibodies and, since the subjects in the transition arm had higher binding anti-drug antibodies at week 16 due to re-randomization, this resulted in higher neutralizing anti-drug antibodies by the end of the study.

**Figure 10. Study 20120263 Binding and Neutralizing Anti-drug Antibodies Summary Results From Week 16 Through Week 52**



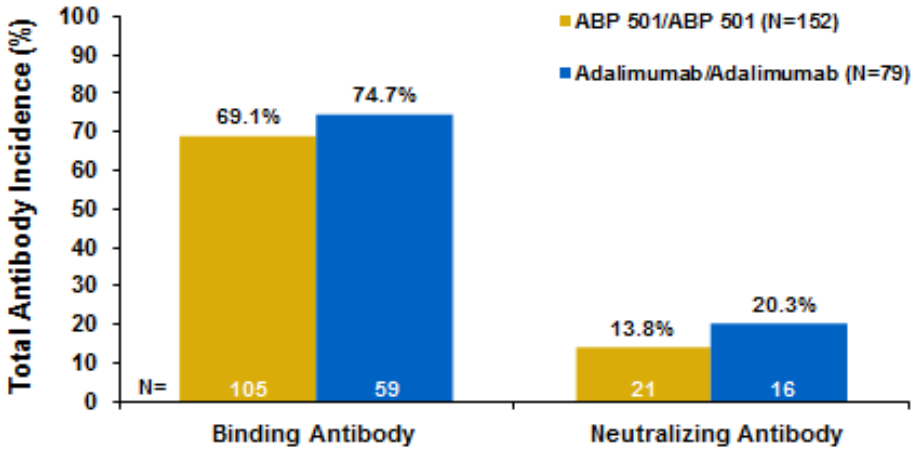

To further evaluate any potential effect of transitioning from adalimumab to ABP 501, a post-hoc analysis of the rate of anti-drug antibody development was performed on the subjects who were anti-drug antibody-negative through week 16. This provided an assessment of any effect without bias introduced by existing anti-drug antibodies. After transitioning from adalimumab to ABP 501, the incidence of new anti-drug antibodies in these subjects was similar to non-transitioned subjects (Figure 11). None of the subjects who were anti-drug antibody-negative through week 16 developed neutralizing antibodies by the time of the last assessment at week 52.

**Figure 11. Study 20120263 Binding Anti-drug Antibodies Summary Results Week 20 to Week 52 for Subjects Anti-drug Antibody-negative Through Week 16**




Finally, the data presented in Figure 12 shows the rate of binding and neutralizing anti-drug antibodies for subjects who maintained treatment with ABP 501 or adalimumab through week 52. The percentage of subjects positive anytime in the study for binding and neutralizing antibodies was comparable through week 52, regardless of treatment received.

**Figure 12. Study 20120263 Binding and Neutralizing Anti-drug Antibodies Summary Results Anytime from Week 0 to Week 52**



## Conclusion

Based on the totality of evidence from the ABP 501 biosimilar development program, Amgen concludes that:

1. ABP 501 is highly similar to adalimumab notwithstanding minor differences in clinically inactive components.

and

2. There are no clinically meaningful differences between ABP 501 and adalimumab in terms of safety, efficacy, and immunogenicity.

By matching each of the known or plausible mechanisms of action, establishing PK similarity, as well as confirming clinical similarity with respect to safety, efficacy, and immunogenicity in 2 sensitive populations, and considering the knowledge of adalimumab in all approved indications,

Furthermore, by matching each of the known or plausible mechanisms of action and demonstrating clinical similarity in sensitive populations that represent all of those currently approved adalimumab, it can be concluded that ABP 501 will perform equivalently to adalimumab in each of the approved indications. Amgen is therefore seeking approval in all indications of adalimumab that are not subject to remaining regulatory exclusivity:

- rheumatoid arthritis
- juvenile idiopathic arthritis in patients 4 years of age and older
- psoriatic arthritis
- ankylosing spondylitis
- adult Crohn's disease
- ulcerative colitis
- plaque psoriasis

## 2. BACKGROUND INFORMATION

### 2.1 Section 351(k) Regulatory Pathway for Biosimilars

The Biologics Price Competition and Innovation Act of 2009 created an abbreviated licensure pathway for biological products shown to be highly similar to an FDA-licensed biological product (also known as the reference product). Section 351(k) allows a biosimilar sponsor to rely on existing scientific knowledge about the safety and efficacy of the reference product, and consequently enables a biosimilar biological product to be licensed based on less than a full complement of product-specific nonclinical and clinical data typically required under the section 351(a) regulatory pathway (ie, an innovative biologics license application).

Section 351(k) defines the terms “biosimilar” or “biosimilarity” to mean that:

> the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components

and

> there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product

Statutory requirements mandate that a biosimilar product must have the same primary sequence, mechanism of action, route of administration, dosage form, and strength as the reference product. A 351(k) application for licensure of the biosimilar must contain, among other things, information demonstrating that the proposed product is highly similar to its reference product. This demonstration is typically based on data derived from comparative analytical studies, animal studies, and a clinical study in an appropriate condition of use. If the biological product meets the statutory requirements for licensure as a biosimilar product under section 351(k), the potential exists for the biosimilar to be licensed for additional conditions of use (eg, indications) for which the reference product is licensed that were not studied during the biosimilar development program. This concept is referred to as extrapolation of indications and must be justified based on scientific evidence in the 351(k) application.

The development of a biosimilar product under section 351(k) differs from the development of an innovative biological product intended for submission under section 351(a) in regards to the intent, types, and scopes of studies performed. While both innovative and biosimilar development programs generate analytical, nonclinical, and clinical data, the number and types of studies conducted will differ based on the differing goals and the different statutory requirements for licensure of each program.

The purpose of an innovative development program is to establish the efficacy, safety, purity, and potency of the proposed product based on data derived from a full complement of quality, nonclinical, and clinical studies to ultimately establish the risk:benefit profile. The purpose of a biosimilar development program, in contrast, is not to independently establish a risk:benefit profile of the proposed biosimilar product in each indication, but instead is to demonstrate that the proposed biosimilar product is highly similar to the reference product. Therefore, the clinical endpoints and study designs for biosimilars will typically differ from those of innovator development programs. Although the biosimilar nonclinical program is significantly reduced, the biosimilar quality program must meet the same expectations that an innovator is required to, in addition to extensive structural and functional characterization comparisons between the biosimilar and reference product.

The underlying presumption justifying an abbreviated biosimilar development program is that a molecule shown to be structurally and functionally highly similar to a reference product will behave like the reference product in the clinical setting. However, biological products are structurally and functionally complex and certain clinical aspects (eg, immunogenicity) cannot be predicted with analytical and nonclinical comparative testing alone. Therefore, a clinical study in a relevant and sensitive population is necessary for efficacy, safety, and immunogenicity comparisons to support biosimilar licensure. To demonstrate biosimilarity, FDA has recommended that sponsors use a "stepwise approach" to develop the data and information needed for the biosimilar product's licensure.

The stepwise approach begins with an extensive structural and functional characterization of the proposed biosimilar product and the reference product, and serves as the foundation of the biosimilar development program, as well as informing extrapolation. An assessment is then made regarding the analytical similarity of the proposed biosimilar product to the reference product, based on the structural and functional characterization results. During this assessment, an analysis of any differences and their potential to be clinically meaningful is made. Amgen conducted an extensive analytical similarity assessment program comparing ABP 501 to adalimumab to address each of the points above, and determined that ABP 501 is analytically highly similar to adalimumab (Section 3).

In the next step, a nonclinical assessment is performed. The results must demonstrate a lack of unexpected effects with the biosimilar, as compared to the reference product, and

can provide more supporting information in the biosimilarity determination. Amgen conducted a nonclinical study in cynomolgus monkeys with the objectives of assessing toxicokinetic similarity, demonstrating a lack of unexpected effects with ABP 501, and comparing the toxicity of ABP 501 to adalimumab. The results showed ABP 501 to be similar to adalimumab (Section 4).

The last step in the stepwise approach is a targeted clinical program. Particularly, clinical studies in this step must be performed in sensitive populations and be designed to allow for the detection of any clinically meaningful differences. Additionally, the population studied can inform the use of the biosimilar in other indications of the reference product and thereby provide additional scientific justification for the extrapolation of indications. The purpose of the clinical program is to address any residual uncertainty remaining with respect to any analytical differences and to confirm that such differences are not clinically meaningful. The clinical similarity of ABP 501 and adalimumab was established, in terms of PK, safety, efficacy, and immunogenicity, (Section 5).

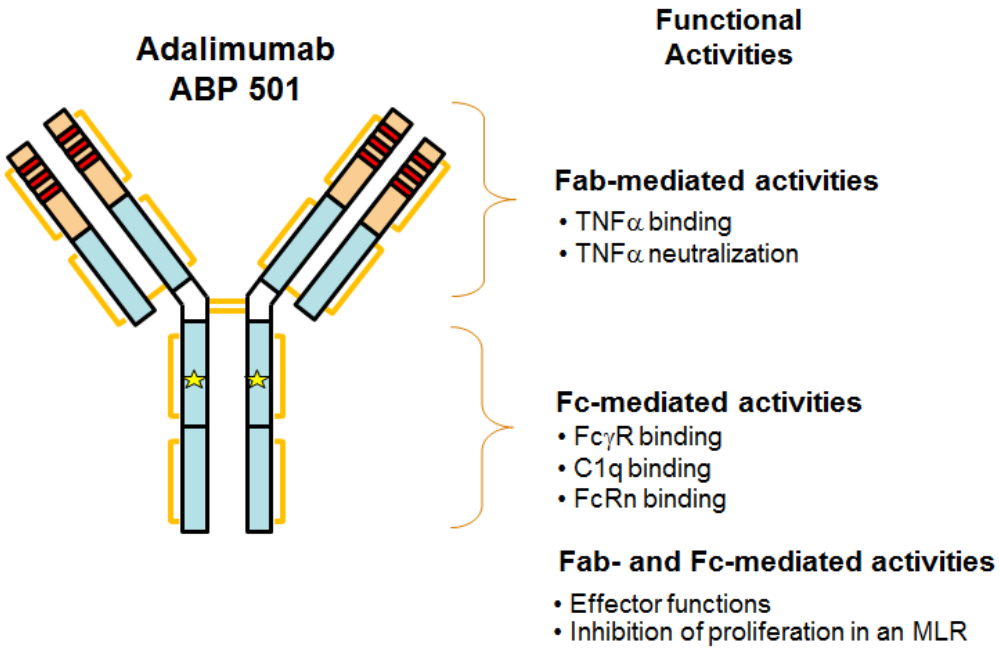
When the analytical, nonclinical, and clinical results are assessed holistically (ie, the "totality of the evidence"), the FDA can then evaluate whether an applicant has adequately demonstrated that a proposed biosimilar product meets the statutory requirement for biosimilarity to the reference product. During the evaluation, the FDA can determine that extrapolation to other indications not studied during the sponsor's biosimilar development program is appropriate if a scientifically rigorous justification is provided. Key points considered to support ABP 501's extrapolation to adalimumab's approved indications are addressed in each section of this document, with an overall summary provided in Section 6.

## 2.2 Product Knowledge

### 2.2.1 Structural and Functional Characteristics

Adalimumab and ABP 501 are human immunoglobulin isotype G subclass 1 (IgG1) monoclonal antibodies against TNFα. Both products are expressed in Chinese hamster ovary cell lines, although each cell line is different and proprietary to the manufacturer. The antibodies consist of 2 heavy chains and 2 light chains, including 32 cysteine residues that are involved in both intra-chain and inter-chain disulfide bonds (Figure 13). Each heavy chain contains an N-linked glycan at a consensus site in the Fc region, which is the site for glycosylation.

**Figure 13. Adalimumab and ABP 501 Functional Attributes**




C1q = complement component 1,q; Fab = fragment antigen binding; Fc = fragment crystallizable; FcγR = Fc-gamma receptor; FcRn = neonatal Fc receptor; MLR = mixed lymphocyte reaction; TNFα = tumor necrosis factor alpha.

Yellow lines represent disulfide bonds. Red rectangles represent the complementarity-determining region. Yellow stars represent glycosylation sites.

An IgG1 antibody can generally be described as consisting of 2 main regions, the fragment antigen binding (Fab) region and the fragment crystallizable (Fc) region (Figure 13). Each region is responsible for mediating distinct functional activities. Binding to an antigen is mediated by the complementarity-determining region located in the Fab domain of the antibody. The Fc region, in contrast, mediates effector functions by binding to either Fcγ receptors on immune cells or to complement components. When binding to Fc receptors or complement components occurs concurrently with binding to antigen on the membrane of target cells, the antigen-driven clustering of the antibody can lead to effector cell activation. This effector cell activation can result in activities such as ADCC and CDC. The Fc region is also responsible for modulating antibody recycling via neonatal Fc receptor (FcRn) binding, and consequently affects the levels of antibody present in blood.

In contrast to small molecules, which are generally a single chemical entity, monoclonal antibodies typically exhibit a degree of structural heterogeneity. This heterogeneity is caused by the complexity and inherent variability of protein production in a living system. Depending on the degree of the heterogeneity, and where structural variations occur in

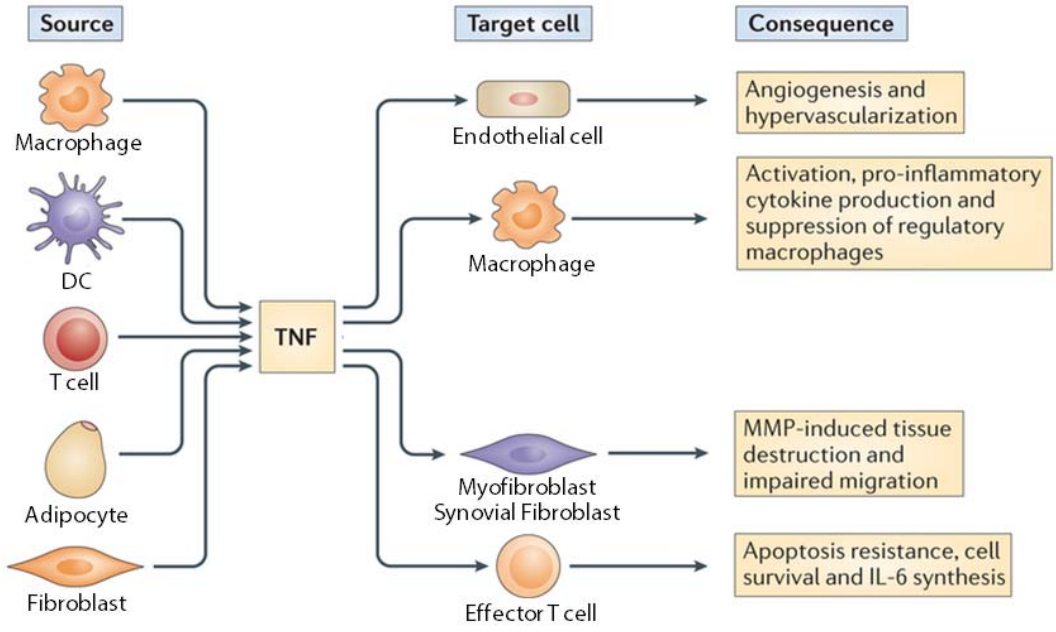
the antibody, this heterogeneity can either have no clinical impact, or it may affect the safety, efficacy, or immunogenicity of a product.

Given that a degree of heterogeneity is expected in all biologic products and since a biosimilar is manufactured using a different cell line and process, minor differences in structural and purity attributes are expected between a biosimilar and its reference product. Amgen performed a comprehensive characterization for the structural and purity attributes of ABP 501 and adalimumab as a first step in the analytical similarity assessment (Section 3). In addition to assessing any variations in structural and purity attributes, Amgen also evaluated if differences, where observed, could be expected to affect safety, efficacy, and immunogenicity of the product. Despite any minor structural differences, all clinically relevant functional activities of a biosimilar should be similar to its reference product. Accordingly, the functional activities of ABP 501 were measured using sensitive assays selected to capture all of the known or plausible mechanisms of action for adalimumab in each of the approved indications (Section 3.2.2).

### 2.2.2 Background on the Biology of TNFα

TNFα is a master cytokine that regulates a carefully controlled immune response to infection or injury. Although it is widely expressed, monocytes and macrophages are considered the primary source of TNFα production during an inflammatory response (Figure 14).

**Figure 14. Pathogenic Role of TNFα, a Master Cytokine**




DC = dendritic cell; IL-6 = interleukin-6; MMP = matrix metalloproteinase; TNF = tumor necrosis factor.

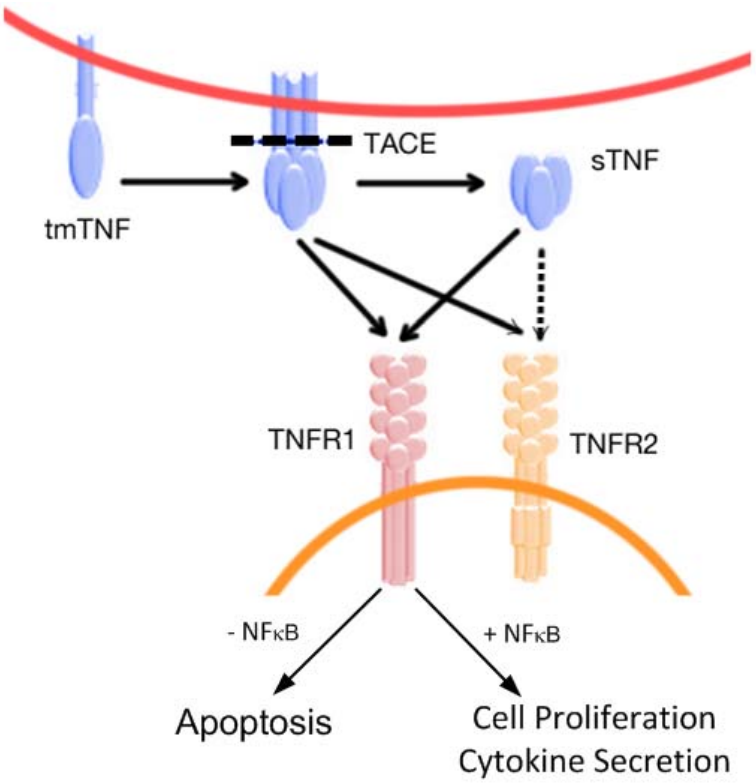
Adapted from Neurath, 2014.

TNFα exists in 2 biologically active forms:

- a soluble trimeric form (referred to as soluble TNFα or TNFα)
- a membrane-bound trimeric form (referred to as transmembrane TNFα)

Soluble TNFα is generated from transmembrane TNFα following cleavage by TNFα-converting enzyme (Figure 15). Under normal physiological conditions, the concentration of soluble TNFα found in bodily fluids is almost undetectable. However, stimulation by an immune challenge, or induction via the pathophysiology of certain autoimmune diseases, can increase soluble TNFα concentrations to measurable, and sometimes very high levels. Levels of transmembrane TNFα are generally low regardless of the state of inflammation because cleavage to form soluble TNFα occurs rapidly.

**Figure 15. Simplified Representation of the Structure and Forms of TNFα and TNFRs**




NFκB = nuclear factor kappa-light-chain-enhancer of activated B cells; sTNF =soluble tumor necrosis factor; TACE = tumor necrosis factor alpha converting enzyme; tmTNF =transmembrane tumor necrosis factor; TNFR = TNF receptor.

Adapted from https://ca.w kipedia.org/wiki/Fitxer:TNF.png

Biological responses to soluble TNFα and transmembrane TNFα are mediated through 2 structurally distinct cell surface TNFα receptors (Figure 15):

- TNFR1 (also known as p55 cell surface TNF receptor)
- TNFR2 (also known as p75 cell surface TNF receptor)

TNFR1 is widely expressed and is recognized as the primary signaling receptor for soluble TNFα (Tracey et al, 2008). When activated by soluble TNFα, TNFR1 mediates diverse activities, including pro-inflammatory gene expression, cellular proliferation, or apoptosis (Figure 15). The outcome of soluble TNFα signaling depends largely on the basal state of nuclear factor kappa light chain enhancer of activated B cells (NFκB) signaling in the responding cell (Micheau and Tschopp, 2003; Pimentel-Muiños and Seed, 1999). NFκB is a transcription factor that, among other things, induces anti-apoptotic proteins. When NFκB is inactive, TNFα signaling will lead to apoptosis and other types of cell death. In contrast, when NFκB is active, TNFα signaling results in the expression of anti-apoptotic proteins, and thus will lead to pro-inflammatory responses, such as the induction of proliferation or cytokine secretion (Figure 15).

TNFR2 is expressed primarily on T cells and endothelial cells. Molecular signaling events mediated by TNFR2 are not as well understood as those mediated by TNFR1, however transmembrane TNFα is considered the primary activating ligand for TNFR2 (Slevin and Egan, 2015).

In addition to engaging TNFR1 and TNFR2, transmembrane TNFα has been reported to transmit intracellular signals back to the expressing cell when engaged by its receptor, a process termed “reverse signaling.” The exact mechanism for reverse signaling is not fully understood, and reported activities have not always been reproducible (Slevin and Egan, 2015). Reverse signaling may mediate additional inflammatory and anti-inflammatory responses in some cell types expressing transmembrane TNFα (Horiuchi et al, 2010).

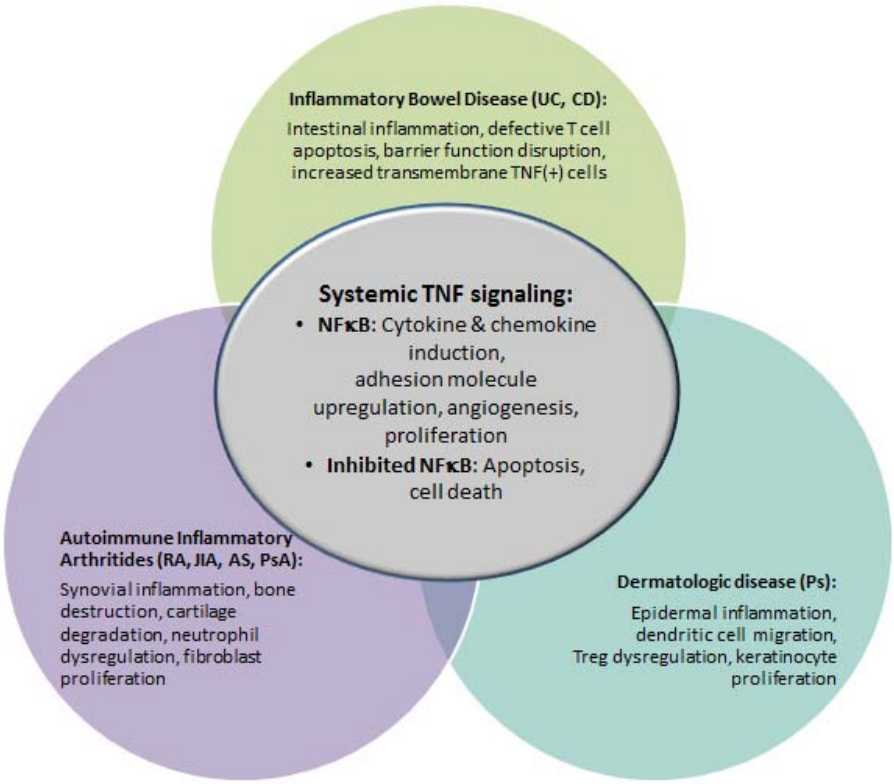
### 2.2.3 Mechanism of Action for ABP 501 and Adalimumab

Given its importance in mediating an immune response, it is expected that dysregulation of TNFα activity can result in pathogenic effects and would play a central role in autoimmune disease initiation and maintenance (Figure 14). Overexpression of TNFα in disease settings results in a diverse range of consequences, including the activation of additional pro-inflammatory cytokines, increased T cell survival, suppression of regulatory macrophages, endothelial cell dysfunction, and tissue destruction. The Fab

regions of adalimumab and ABP 501 bind with high affinity and specificity to the antigen TNFα (Figure 13). The primary mechanism of action of adalimumab and ABP 501 is the neutralization of these diverse pro-inflammatory activities mediated by soluble TNFα.

Some of the TNFα-induced pro-inflammatory consequences in disease (Figure 14) are the result of systemic TNFα overexpression, and thus can be considered common to all the autoimmune diseases for which adalimumab is approved (central gray area of Figure 16). Systemic effects of elevated soluble TNFα activity are evident through induction of the acute phase inflammatory response and elevation of C-reactive protein, a key acute phase protein, which can be observed in patients in the majority of indications in which adalimumab is approved for use. The diverse cellular outcomes induced by TNFα are the result of carefully controlled molecular pathways in the responding cells (Figure 15). For instance, when soluble TNFα engages TNFR1 in the context of active NFκB, it will induce pro-inflammatory signaling including the induction of multiple cytokines and chemokines, increased adhesion molecule expression, proliferation, tissue injury, and angiogenesis (Figure 14). Alternatively, in other cellular contexts when NFκB inactive, and thus lower expression of anti-apoptotic proteins, apoptosis occurs in response to stimulation by soluble TNFα. Both the pro-inflammatory and apoptotic signaling outcomes are fundamental TNFα-mediated activities and are common to the autoimmune diseases in which adalimumab is approved to treat.

**Figure 16. Schematic Summary of the Role of TNFα in the Pathogenesis of Disease**




AS = ankylosing spondylitis; CD = Crohn's disease; JIA = juvenile idiopathic arthritis; NFκB = nuclear factor kappa-light-chain-enhancer of activated B cells; PsA = psoriatic arthritis; Ps = plaque psoriasis; RA = rheumatoid arthritis; TNF(+) = tumor necrosis factor positive; Treg = regulatory T cell; UC = ulcerative colitis.

Some effects mediated by soluble TNFα are a consequence of local overexpression and are thus specific to particular autoimmune diseases, as depicted in the outlying circles in Figure 16. For example, in the autoimmune inflammatory arthritides (rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and juvenile idiopathic arthritis), TNFα is overexpressed in the synovium and influences local inflammation, bone destruction, cartilage degradation, and synovial fibroblast proliferation primarily through NFκB-dependent signaling (Romas et al, 2002). As concluded from literature for adalimumab and knowledge gained from clinical testing of different TNF-inhibitors in autoimmune disease, the arthritides share common molecular mechanisms of soluble TNFα-driven signaling and resulting pathologies in the joint that are normalized by adalimumab.

Activities specific to inflammatory dermatologic disease (plaque psoriasis) include local effects on keratinocyte proliferation leading to epidermal thickening, dendritic cell migration and activation, and reduction of regulatory T cell activity which all contribute to skin pathology (Keijsers et al, 2015; Victor et al, 2003). Inhibition of soluble TNFα-driven

signaling is also the primary adalimumab mechanism of action in inflammatory dermatologic disease, where it is able to down-modulate pro-inflammatory NFκB-dependent signaling in affected skin.

In the inflammatory bowel diseases (ulcerative colitis and Crohn's disease), soluble TNFα not only mediates intestinal inflammation but also leads to a disruption of barrier function, which activates the innate immune system in additional ways due to bacteria exposure within the lumen of the gut (Fischer et al, 2013). Defective T cell apoptosis is associated with Crohn's disease and T cell apoptosis is restored following treatment with anti-TNF agents (Peake et al, 2013).

In addition, elevated levels of transmembrane TNFα-positive macrophages and T cells can be visualized during colonoscopy in Crohn's disease patients (Atreya et al, 2014). The investigators demonstrated that adalimumab responders have higher numbers of cells expressing transmembrane TNFα prior to treatment when compared to non-responders, suggesting a potential role for transmembrane TNFα expressing cells in Crohn's disease. Therefore, their depletion may contribute to another mechanism of action of adalimumab. Additionally, adalimumab is able to induce regulatory macrophage function in vitro, as measured by a mixed lymphocyte reaction. This is another process that relies on transmembrane TNFα expression (Vos et al, 2011) and may contribute to the reduction in tissue resident inflammatory cells associated with the clinical efficacy of adalimumab. As another means of reducing the number of transmembrane TNFα-expressing cells, adalimumab has been demonstrated to mediate ADCC and CDC of transmembrane TNFα expressing cells in vitro (Arora et al, 2009). The binding of adalimumab to transmembrane TNFα could contribute to clinical efficacy via cell depletion (ADCC and CDC), decreased cellular proliferation (increased regulatory macrophage function), or a combination of the different mechanisms.

In summary, ABP 501 and adalimumab modulate the activity of TNFα by essentially 2 mechanisms. By binding to soluble TNFα, the antibody blocks the activity of the pro-inflammatory cytokine and thus decreases the inflammatory response. This activity is fundamental to efficacy in all approved adalimumab indications. The second mechanism involves reducing the number of transmembrane TNFα-positive cells, which might be relevant in the inflammatory bowel disease indications. The antibody may reduce transmembrane TNFα-positive cells by mechanisms such as induced cytotoxicity (via ADCC or CDC) or reducing further proliferation through the induction of regulatory

macrophages. As discussed below, the mechanisms of action knowledge was taken into account when designing the functional testing aspects of the analytical similarity assessment.

### 2.2.4 Incorporation of Adalimumab Product Knowledge into the ABP 501 Biosimilar Development Program

Information on the known adalimumab mechanisms of action in each indication, as well as current adalimumab product knowledge, was applied during the design of the analytical similarity testing of ABP 501. The first focus was on assessing similarity in structural and purity attributes. This structural and purity assessment was followed by a comprehensive evaluation of all known functional activities.

To assess the functional similarity of ABP 501 to adalimumab, the testing focused on the primary mechanism of action, ie, the binding to and neutralization of soluble TNFα activity. As discussed above, soluble TNFα induces diverse cellular responses. Therefore, the similarity between ABP 501 and adalimumab was assessed in multiple cell types and with pro-inflammatory (NFκB-dependent) and induced cell death (NFκB-independent) endpoints (Table 3).

The functional similarity assessment also included additional activities, such as binding to transmembrane TNFα, induction of ADCC and CDC, and inhibition of cellular proliferation in a mixed lymphocyte reaction, which may contribute to efficacy in the inflammatory bowel disease indications. The additional activities assessed were compared since they reflect mechanisms by which transmembrane TNFα-expressing cells are reduced or eliminated. A summary of the known and plausible adalimumab mechanisms of action is provided in Table 3. As discussed in Section 3, the analytical similarity assessment results form the basis for Amgen's conclusion that ABP 501 is highly similar to adalimumab and that ABP 501 is expected to perform similarly in all indications approved for adalimumab.

**Table 3. Known and Plausible Mechanisms of Action of Adalimumab in the Approved Conditions of Use**

| | RA, JIA, AS, PsA | Ps, HS | CD, UC | Biological Assays |
|---|---|---|---|---|
| Mechanisms involving Fab region of the antibody – common to all indications | | | | |
| Soluble TNFα binding | Known | Known | Known | ELISA binding method |
| | | | | Binding kinetics by SPR |
| Soluble TNFα neutralization | Known | Known | Known | Apoptosis inhibition |
| | | | | Inhibition of IL-8 induction (HUVEC) |
| | | | | Inhibition of cytotoxicity |
| | | | | Inhibition of chemokine induction (blood) |
| Mechanisms involving Fab (transmembrane TNF) and Fc regions of the antibody – may be important in inflammatory bowel disease indications | | | | |
| Transmembrane TNFα binding | - | - | Plausible | Competitive cell-based assay |
| Effector functions | - | - | Plausible | Induction of CDC |
| | | | | Induction of ADCC |
| Modulation of immune cells expressing transmembrane TNFα | - | - | Plausible | Inhibition of proliferation in a mixed lymphocyte reaction |

ADCC = antibody-dependent cellular cytotoxicity; AS = ankylosing spondylitis; CD = Crohn's disease; CDC = complement dependent cytotoxicity; ELISA = enzyme-linked immunosorbent assay; Fab = fragment antigen binding; Fc = fragment crystallizable; HS = hidradenitis suppurativa; HUVEC = human umbilical vein endothelial cells; IL-8 = interleukin 8; JIA = juvenile idiopathic arthritis; NF B = nuclear factor kappa light chain enhancer of activated B cells; PsA = psoriatic arthritis; Ps = plaque psoriasis; RA = rheumatoid arthritis; SPR = surface plasmon resonance; UC = ulcerative colitis.

## 2.3 ABP 501 Manufacturing Information

Amgen undertook a thorough process to develop a cell line for ABP 501 to ensure that ABP 501 would match the amino acid sequence and other important structural and functional characteristics of adalimumab. In doing this, a large number of clones were screened before creating the ABP 501 cell bank.

The ABP 501 commercial manufacturing process was developed and implemented prior to the initiation of clinical trials. Manufacturing changes were minimized during development to reduce potential shifts in product quality that could confound a determination of biosimilarity. Notably, the commercial drug substance manufacturing site and scale were used for the manufacture of the lots used in the clinical trials.

The ABP 501 drug substance manufacturing process consists of cell culture, harvest, and purification steps, including steps designed to inactivate or remove any potential viral contaminants and to reduce process-related impurities acceptable levels. The ABP 501 drug substance manufacturing process was validated and consistently meets process performance and product quality expectations.

ABP 501 drug product is supplied as a sterile, preservative-free solution for subcutaneous administration. The ABP 501 formulation was selected based on Amgen's experience with similar products, and uses excipients common in injectable products. ABP 501 is formulated at the same drug substance concentration as adalimumab but uses different excipients, including different buffer components and stabilizers. The analytical, nonclinical, and clinical similarity assessments demonstrated that the formulation difference has no effect on the similarity between ABP 501 and adalimumab.

The drug product will be available in the following 3 presentations:

- a prefilled syringe containing 20 mg (0.4 mL)
- a prefilled syringe containing 40 mg (0.8 mL)
- a prefilled syringe assembled with an autoinjector, containing 40 mg (0.8 mL)

The 40 mg prefilled syringe presentation was used in the clinical trials but all 3 presentations have the same formulation and exhibit comparable quality and stability. Additionally, to support introduction of the autoinjector, Amgen evaluated device functionality/performance in line with current International Organization for Standardization requirements and conducted Human Factors Engineering and Usability Engineering studies. The studies demonstrated the suitability and usability of the autoinjector device and that patients can effectively follow the instructions for use. Each of the commercial presentations is intended to provide a single, fixed dose for subcutaneous injection by a health care professional, caregiver, or patient. The ABP 501 drug product manufacturing process was validated and consistently meets process performance and product quality expectations.

## 3. ANALYTICAL SIMILARITY

The analytical similarity assessment comparing adalimumab and ABP 501 was conducted according to a testing plan that pre-specified the analyses to be performed and the assessment criteria to be applied when evaluating the similarity between the products.

To perform the analytical similarity assessment, adalimumab lots were procured over approximately 6 years to estimate the lot-to-lot variability of adalimumab. The ABP 501 lots used for analysis were manufactured between 2011 and 2015. Testing included 24 adalimumab (US) and 18 adalimumab (EU) lots (which included 5 lots each of adalimumab [US] and adalimumab [EU] used in the clinical trials), and 10 ABP 501 lots. The ABP 501 lots included those used in the nonclinical studies, all lots used in the clinical trials, and lots from process validation. The number of lots analyzed for each method was defined based on attribute criticality and the influence of the manufacturing process on the attribute.

The discussion of analytical similarity provided in this section focuses on the comparison of ABP 501 to adalimumab (US); however, Amgen used both adalimumab (US) and adalimumab (EU) in the clinical program (Section 5). Therefore, Amgen compared adalimumab (US) and adalimumab (EU) analytically and in a PK similarity study in order to establish a scientific bridge (Section 1). To complete the analytical comparisons, ABP 501, adalimumab (US), and adalimumab (EU) were subjected to the same testing plan. The analytical similarity results between adalimumab (US) and adalimumab (EU) provided in the biologics license application, when combined with the 3-way PK similarity data (Section 5.2.1), established the equivalence of adalimumab sourced from the 2 regions.

The attributes studied in the analytical similarity assessment were selected based on knowledge regarding the structure, function, and heterogeneity of adalimumab and ABP 501, including those characteristics critical to the biological activity and stability of the products (Section 2.2). The assessment included comparative evaluations and incorporated complimentary structural, purity, and functional methods that measured the same attribute from different scientific perspectives. Amgen employed state-of-the-art, sensitive assays to distinguish product attributes. All of the methods were appropriately qualified or validated, and determined to be suitable for their intended use.

### 3.1 Tiering of the Analytical Similarity Attributes

During the course of the ABP 501 development program, the FDA recommended using a risk-ranking approach to tier attributes/assays. In agreement with FDA advice, each similarity attribute/assay was assigned to 1 of 3 tiers based on the relevance of the attribute to clinical outcomes and the nature of the data output from the analysis.

Tier 1 attributes/assays have the highest risk to clinical outcomes, and include assays that evaluate the primary mechanism(s) of action that are known to contribute to the safety and efficacy profile. Specifically, potency (as determined by an apoptosis inhibition bioassay) and binding to soluble TNF$\alpha$ are directly relevant to the primary mechanism of action and were categorized as Tier 1 by agreement with the FDA. Tier 1 attributes/assays were assessed using statistical equivalence. Under this approach, similarity is concluded when the 90% confidence interval for the difference in means between the products is contained within an equivalence acceptance criterion (EAC) of $\pm$ 1.5 times the standard deviation of the dataset for the reference product lots tested.

Tier 2 attributes/assays have a relatively lower risk to clinical outcomes and include other mechanisms of action, structural attributes, product strength, and product-related substances and impurities. The Tier 2 attributes/assays were considered to be similar between the products when 90% of the ABP 501 lots fell within a pre-defined quality range established based on the dataset for the reference product lots tested. The quality range was defined as the mean of the reference product lots tested $\pm$ 3 standard deviations. For Tier 2 attributes/assays where a change over time was observed at the recommended storage condition, all values were adjusted for material age prior to the quality range assessment. This was achieved by calculating the mean rate of change over time for the attribute, and then extrapolating all results to the end of the proposed shelf-life, in order to allow a comparison that would not be biased by sample age effects. For Tier 2 attributes/assays where the data were not amenable to statistical evaluation, individual values were compared to a pre-defined limit, which was based on the method capability and/or attribute criticality, and similarity was demonstrated if every individual value satisfied the limit.

Tier 3 attributes/assays included those with the lowest risk to clinical outcomes, and those where the data are qualitative or not suitable for numerical evaluations, such as profile comparisons. Similarity of Tier 3 attributes was based on qualitative comparisons.

## 3.2 Analytical Similarity Results

### 3.2.1 Structural and Purity Attributes

The structure and purity of ABP 501 and adalimumab were compared using assays that assessed the following categories: primary structure, higher order structure, particles and aggregates, product-related substances and impurities, thermal stability and forced degradation profile, general properties, and process-related impurities.

The structural and purity results are presented in Table 4 and demonstrate that ABP 501 is analytically similar to adalimumab. In the table, a check mark indicates that the pre-defined similarity assessment criteria were met. Where this was not the case, the observed difference is noted in the table. Representative analytical data that can be presented graphically are shown in Appendix 1.

## Table 4. ABP 501 vs Adalimumab (US) Analytical Similarity Assessment Results for Structural and Purity Characteristics

| Category | Analytical Testing and Parameter | Tier - Similarity Assessment Approach | Assessment Criteria | ABP 501 Results | Demonstrated Similarity |
|---|---|---|---|---|---|
| Primary Structure | Intact molecular mass: Profile | 3 - Qualitative comparison | N/A | Visually similar[a], Figure 51 | √ |
| | Intact molecular mass: Molecular weight | 2 – Pre-defined limit | Observed mass should be within ± 50 ppm of the theoretical mass for the predominant species | Predominant species all within 50 ppm of the theoretical masses | √ |
| | Reduced and deglycosylated molecular masses of HC and LC: Profile | 3 - Qualitative comparison | N/A | Visually similar[a], Figure 52, Figure 53 | √ |
| | Reduced and deglycosylated molecular masses of HC and LC: Molecular weight | 2 – Pre-defined limit | Observed mass should be within ± 50 ppm of the theoretical mass | Observed mass was within 50 ppm of the theoretical mass | √ |
| | Reduced peptide map: Profile | 3 - Qualitative comparison | N/A | Visually similar[a], Figure 54 | √ |
| | Reduced peptide map: amino acid sequence | 2 – Pre-defined limit | Observed mass of the tryptic peptide fragments should be within ± 15 ppm of the theoretical mass | Observed mass was within 15 ppm of the theoretical mass | √ |
| | Non-reduced peptide map: Profile | 3 - Qualitative comparison | N/A | Visually similar[a], Figure 55 | √ |
| | Non-reduced peptide map: Disulfide containing peptides and reduced peptides | 2 – Pre-defined limit | Observed mass of the tryptic peptide fragments should be within ± 15 ppm of the theoretical mass for peptides ≤ 10,000 Da and within ± 100 ppm for peptides > 10,000 Da | Observed mass was within ± 15 ppm of the theoretical mass for peptides ≤ 10,000 Da and within ± 100 ppm for peptides > 10,000 Da | √ |



Abbreviations defined on last page of this table.

[a] Visually similar = no new peaks/species greater than the detection limit of the method.
[b] For Tier 2 attr butes using a quality range, analytical similarity was demonstrated if at least 90% of the individual test lot values fell within the adalimumab derived quality range.

## Table 4. ABP 501 vs Adalimumab (US) Analytical Similarity Assessment Results

| Category | Analytical Testing and Parameter | Tier - Similarity Assessment Approach | Assessment Criteria | ABP 501 Results | Demonstrated Similarity |
|---|---|---|---|---|---|
| Primary Structure | Glycan map: Profile | 3 - Qualitative comparison | N/A | Visually similar[a], Figure 56 | √ |
| | Glycan map: % total afucosylation | 2 - Quality range[b] | 7.5 to 13.3 | 6.7 to 10.8 | √ |
| | Glycan map: % high mannose | 2 - Quality range[b] | 5.6 to 10.6 | 5.0 to 8.5 | Minor quantitative differences in specific glycans (Section 3.2.1.1) |
| | Glycan map: % afucosylation | 2 - Quality range[b] | 1.0 to 1.9 | 1.6 to 2.4 | |
| | Glycan map: % galactosylation | 2 - Quality range[b] | 16.5 to 23.0 | 19.9 to 39.2 | |
| | Glycan map: % sialylation | 2 - Quality range[b] | 0.1 to 0.3 | 0.5 to 1.2 | |
| | cIEF: Profile | 3 - Qualitative comparison | N/A | Visually similar[a], Figure 57 | √ |
| | cIEF: Isoelectric point | 2 – Pre-defined limit | ± 0.07 pH units | The average main peak pI value were within 0.07 pH units | √ |
| | Extinction coefficient | 2 – Pre-defined limit | ± 10% | Within 10% | √ |
| | Identity by ELISA | 3 - Qualitative comparison | N/A | Similar | √ |

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Abbreviations defined on last page of this table.

[a] Visually similar = no new peaks/species greater than the detection limit of the method.
[b] For Tier 2 attr butes using a quality range, analytical similarity was demonstrated if at least 90% of the individual test lot values fell within the adalimumab derived quality range.

## Table 4. ABP 501 vs Adalimumab (US) Analytical Similarity Assessment Results

| Category | Analytical Testing and Parameter | Tier - Similarity Assessment Approach | Assessment Criteria | ABP 501 Results | Demonstrated Similarity |
|---|---|---|---|---|---|
| Higher Order Structure | FTIR: Spectral similarity | 2 – Pre-defined limit | Spectral similarity is ≥ 95% | Spectral similarity value of each individual lot is > 95% when compared to the reference spectrum | √ |
| | FTIR: Profile | 3 - Qualitative comparison | N/A | Visually similar[a], Figure 58, Figure 59 | √ |
| | Near UV CD: Spectral similarity | 2 – Pre-defined limit | Spectral similarity is ≥ 95% | Spectral similarity value of each individual lot is > 95% when compared to the reference spectrum | √ |
| | Near UV CD: Profile | 3 - Qualitative comparison | N/A | Visually similar[a], Figure 60, Figure 61 | √ |
| | DSC: Profile | 3 - Qualitative comparison | N/A | Visually similar[a], Figure 62 | √ |
| | DSC: $T_{m1}$ | 2 - Quality range[b] | 71.3 to 72.5 | 71.7 to 72.1 | √ |
| | DSC: $T_{m2}$ | 2 - Quality range[b] | 82.0 to 83.4 | 82.2 to 82.7 | √ |

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Abbreviations defined on last page of this table.

[a] Visually similar = no new peaks/species greater than the detection limit of the method.
[b] For Tier 2 attr butes using a quality range, analytical similarity was demonstrated if at least 90% of the individual test lot values fell within the adalimumab derived quality range.

## Table 4. ABP 501 vs Adalimumab (US) Analytical Similarity Assessment Results

| Category | Analytical Testing and Parameter | Tier - Similarity Assessment Approach | Assessment Criteria | ABP 501 Results | Demonstrated Similarity |
|---|---|---|---|---|---|
| Particles and Aggregates | HIAC: ≥ 2 μm particles<br>≥ 5 μm particles<br>≥ 10 μm particles<br>≥ 25 μm particles | 3 - Qualitative comparison | N/A | Similar | √ |
| | MFI: ≥ 5 μm particles | 3 - Qualitative comparison | N/A | Similar | √ |
| | MFI: ≥ 5 μm non-spherical particles | 2 - Quality range[b] | 0 to 197 | 24 to 172 | √ |
| | FFF: Submicron particles | 3 - Qualitative comparison | N/A | Similar | √ |
| | DLS: Submicron particles | 3 - Qualitative comparison | N/A | Similar | √ |
| | AUC-SV: Monomer (%) | 2 - Quality range[b] | 95.8 to 100.0 | 98.4 to 99.9 | √ |
| | AUC-SV: Profile | 3 - Qualitative comparison | N/A | Visually similar[a], Figure 64 | √ |
| | SE-HPLC-LS: Molar mass | 2 – Pre-defined limit | Pre-peak within 10% and main peak within 5% of the expected molar masses | Pre-peak within 10% and main peak within 5% of the expected molar masses | √ |
| | SE-HPLC-LS: Profile | 3 - Qualitative comparison | N/A | Visually similar[a], Figure 65, Figure 66 | √ |

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Abbreviations defined on last page of this table.

[a] Visually similar = no new peaks/species greater than the detection limit of the method.
[b] For Tier 2 attr butes using a quality range, analytical similarity was demonstrated if at least 90% of the individual test lot values fell within the adalimumab derived quality range.

## Table 4. ABP 501 vs Adalimumab (US) Analytical Similarity Assessment Results

| Category | Analytical Testing and Parameter | Tier - Similarity Assessment Approach | Assessment Criteria | ABP 501 Results | Demonstrated Similarity |
|---|---|---|---|---|---|
| Product-related Substances and Impurities | SE-HPLC: Profile | 3 - Qualitative comparison | N/A | Visually similar[a], Figure 67 | √ |
| | SE-HPLC: % HMW | 2 - Age adjusted quality range[b] | 0.3 to 0.5 | 0.3 to 0.6 | √ |
| | rCE-SDS: Profile | 3 - Qualitative comparison | N/A | Visually similar[a], Figure 68 | Similar profile |
| | rCE-SDS: % HC+LC | 2 - Age adjusted quality range[b] | 96.5 to 98.4 | 98.2 to 98.5 | Minor differences in glycan occupancy (Section 3.2.1.4) |
| | rCE-SDS: % NGHC | 2 - Age adjusted quality range[b] | 1.0 to 1.6 | 0.5 to 0.6 | |
| | rCE-SDS: % LMW + MMW | 2 - Age adjusted quality range[b] | 0.2 to 0.8 | 0.5 to 0.8 | √ |
| | nrCE-SDS: Profile | 3 - Qualitative comparison | N/A | Visually similar[a], Figure 69 | Similar profile |
| | nrCE-SDS: % Main peak | 2 - Quality range[b] | 97.7 to 99.2 | 96.7 to 98.7 | Minor differences in partially reduced species (Section 3.2.1.4) |
| | nrCE-SDS: % Pre-peaks | 2 - Quality range[b] | 0.8 to 2.3 | 1.3 to 3.2 | |
| | CEX-HPLC: Profile | 3 - Qualitative comparison | N/A | Visually similar[a], Figure 70 | Similar profile |
| | CEX-HPLC: % Acidic peaks | 2 - Age adjusted quality range[b] | 13.1 to 18.2 | 17.6 to 21.7 | Differences in the levels of C-terminal lysine and the formation of deamidated species (Section 3.2.1.4) |
| | CEX-HPLC: % Main peak | 2 - Age adjusted quality range[b] | 55.7 to 64.1 | 65.8 to 68.0 | |
| | CEX-HPLC: % Basic peaks | 2 - Age adjusted quality range[b] | 19.7 to 29.3 | 10.8 to 16.5 | |

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Abbreviations defined on last page of this table.

[a] Visually similar = no new peaks/species greater than the detection limit of the method.

[b] For Tier 2 attr butes using a quality range, analytical similarity was demonstrated if at least 90% of the individual test lot values fell within the adalimumab derived quality range.

## Table 4. ABP 501 vs Adalimumab (US) Analytical Similarity Assessment Results

| Category | Analytical Testing and Parameter | Tier - Similarity Assessment Approach | Assessment Criteria | ABP 501 Results | Demonstrated Similarity |
|---|---|---|---|---|---|
| Thermal Stability and Forced Degradation | 50°C Forced degradation | 3 - Qualitative comparison | N/A | Similar | √ |
| | 40°C Accelerated stability | 3 - Qualitative comparison | N/A | Similar | √ |
| | 25°C Accelerated stability | 3 - Qualitative comparison | N/A | Similar | √ |
| General Properties | Protein concentration (mg/mL) | 2 - Quality range[b] | 47.3 to 53.2 | 47.9 to 52.6 | √ |
| | Deliverable volume (mL) | 2 - Quality range[b] | 0.79 to 0.82 | 0.79 to 0.81 | √ |
| | Osmolality | 3 - Qualitative comparison | N/A | Similar | √ |
| | pH | 3 - Qualitative comparison | N/A | Similar | √ |
| | Appearance | 3 - Qualitative comparison | N/A | Similar | √ |
| | Color | 3 - Qualitative comparison | N/A | Similar | √ |
| | Clarity | 3 - Qualitative comparison | N/A | Similar | √ |
| | Polysorbate | 3 - Qualitative comparison | N/A | Similar | √ |
| Process-related Impurities | HCP- ELISA | 3 - Qualitative comparison | N/A | Similar | √ |
| | HCP analysis by 2D-DIGE | 3 - Qualitative comparison | N/A | Similar | √ |
| | Protein A – ELISA | 3 - Qualitative comparison | N/A | Similar | √ |
| | Residual DNA – qPCR | 3 - Qualitative comparison | N/A | Similar | √ |

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AUC-SV = analytical ultracentrifugation sedimentation velocity; CEX-HPLC = cation exchange high performance liquid chromatography; CI = confidence interval; cIEF = capillary isoelectric focusing; DSC = differential scanning calorimetry; EAC = equivalence acceptance criterion; ELISA = enzyme linked immunosorbent assay; FTIR = fourier transform infrared spectroscopy; HC = heavy chain; HMW = high molecular weight; LC = light chain; LMW = low molecular weight; MFI = micro flow imaging; MMW = mid molecular weight; NGHC = non glycosylated heavy chain; nrCE-SDS = non reduced capillary electrophoresis – sodium dodecyl sulfate; pI = isoelectric point; rCE-SDS = reduced capillary electrophoresis – sodium dodecyl sulfate; SE-HPLC = size exclusion high performance liquid chromatography; SE-HPLC-LS = size exclusion high performance liquid chromatography with light scattering detection; UV CD = ultraviolet circular dichroism.

[a] Visually similar = no new peaks/species greater than the detection limit of the method.
[b] For Tier 2 attributes using a quality range, analytical similarity was demonstrated if at least 90% of the individual test lot values fell within the adalimumab derived quality range.

#### 3.2.1.1 Primary Structure

An analysis of the primary structure was performed which included assays to assess the amino acid sequence, potential sequence variants, and glycosylation of ABP 501 and adalimumab. Based on the results, Amgen concluded that ABP 501 has the same amino acid sequence as adalimumab, and that there were no differences in sequence variants. The glycosylation profile was similar between ABP 501 and adalimumab, and no new species were present (Figure 56); however, some minor quantitative differences in specific glycans were observed.

**Glycosylation**

The following glycan groups were evaluated, and their potential to affect PK and/or effector functions was assessed:

- % Total afucosylation, which includes all glycan structures lacking core fucose and has the potential to affect ADCC:
  - % High mannose, an afucosylated species, which also has the potential to affect PK
  - % Afucosylation, an afucosylated species other than high mannose, which includes afucosylated complex and hybrid glycans
- % Galactosylation, which has the potential to affect CDC
- % Sialylation, which has the potential to affect ADCC

The glycosylation analysis indicated that ABP 501 had slightly lower levels of high mannose and higher levels of afucosylation, sialyation, and galactosylation. These minor differences, at the levels observed, are not considered clinically meaningful since ABP 501 has a similar PK profile compared to adalimumab (Section 5.2.1.2), and all of the ABP 501 lots have similar functional activities, including ADCC and CDC, compared to adalimumab (Section 3.2.2).

#### 3.2.1.2 Higher Order Structure

For the higher order structure evaluation (the 3-dimensional folding and assembly of the IgG1 chains), a number of spectroscopic techniques were used to assess the similarity of the secondary and tertiary structures. No differences in the higher order structure were observed.

#### 3.2.1.3 Particles and Aggregates

With respect to the particulates and aggregates, a number of methods were employed to assess different size ranges and morphologies. The results demonstrated similarity in

all of the tests performed, and there were no significant differences between ABP 501 and adalimumab.

#### 3.2.1.4 Product-related Substance and Impurities

Amgen determined that the main product-related substances and impurities for ABP 501 were size and charge variants. Levels of size and charge variants are known to differ between production cell lines and to be affected by the manufacturing process. Therefore, a number of highly sensitive assays were employed to detect potential differences. The profiles were similar between ABP 501 and adalimumab, and no new species were present (Appendix 1); however, some small quantitative differences in 3 of the assays were observed.

**Cation Exchange – High Performance Liquid Chromatography (CEX-HPLC)**

The first difference observed was in the charged species, as measured by CEX-HPLC. The observed differences in the acidic, main, and basic peaks are attributed to a 10% difference in the levels of C-terminal lysine between the products. In addition, the formation of deamidated species in the Fc region contributes to the differences observed in the acidic peaks.

Variations in C-terminal lysine levels are common in monoclonal antibodies and are not considered to impact potency, safety, or immunogenicity. Furthermore, C-terminal lysine has been shown to be rapidly removed in vivo, soon after administration of an antibody (Cai et al, 2011). With respect to the deamidated species, the same species are present in both ABP 501 and adalimumab, and the rate of formation of these species was similar between the products. These differences did not impact the relative potency of ABP 501 (Section 3.2.2) and are not considered clinically meaningful.

**Reduced Capillary Electrophoresis – Sodium Dodecyl Sulfate (rCE-SDS)**

The next minor difference observed was that ABP 501 has a higher glycan occupancy than adalimumab, as measured by rCE-SDS. ABP 501 had an approximately 1% lower level of non-glycosylated heavy chain (NGHC) compared to adalimumab, and a corresponding 1% higher level of glycosylated structures indicated by % heavy chain + light chain in Table 4. The NGHC levels could potentially affect effector functions. However, since the magnitude of the difference is small, and the effector functions, ADCC and CDC, were not affected (Section 3.2.2), the difference in glycan occupancy is not considered clinically meaningful.

**Non-reduced Capillary Electrophoresis – Sodium Dodecyl Sulfate (nrCE-SDS)**

A non-reduced capillary electrophoresis technique was used to assess product-related impurities associated with variations in disulfide cross-linking. Partially reduced species, indicated as "% pre-peaks" in Table 4, are missing 1 or more disulfide bond cross-linkages. ABP 501 had slightly higher levels of partially reduced species in the heavy chain compared to adalimumab with a difference of less than 1%, with a concomitant change in fully oxidized species (% main peak). The observed difference is quantitatively small and was confirmed to have no effect on the relative potency or effector functions of ABP 501 (Section 3.2.2).

#### 3.2.1.5 Thermal Stability and Forced Degradation

The product structure in thermal forced degradation experiments was assessed since the degradation behavior of a molecule may highlight structural differences that may not be apparent from other testing. The results showed that ABP 501 and adalimumab have similar forced degradation behavior.

#### 3.2.1.6 General Properties

General properties of the drug product were assessed, and similarity for all of the tested properties was demonstrated. Notably the volume and protein concentration results support the conclusion that ABP 501 and adalimumab have the same strength (Section 2.1).

#### 3.2.1.7 Process-related Impurities

Process-related impurities were assessed, and the results demonstrated that these impurities are reduced to acceptably low levels in ABP 501.

### 3.2.2 Functional Activities

The biological assays performed as part of the analytical similarity assessment were intended to evaluate functional similarity and to support the extrapolation to all of the indications for which Amgen is seeking ABP 501 licensure. Therefore, the functional assessment included multiple assays interrogating activities mediated by both the Fc and the Fab regions of the molecule (Figure 13) as well as assays critical to the known and plausible mechanisms of action in all indications in which adalimumab is approved (Table 3). For critical functional assays, and bioactivities that are sensitive to process conditions, 10 ABP 501 lots were tested along with > 10 adalimumab lots. Additional characterization assays were included to comprehensively assess the similarity of the products by testing a representative, but more limited, set of ABP 501 and adalimumab

lots. The results from this assessment confirmed that ABP 501 and adalimumab have similar functional activities.

Results for TNFα binding and potency with respect to neutralization of soluble TNFα were assessed using Tier 1 criteria (Section 3.1). These evaluations served as rigorous tests of similarity in functions directly relevant to clinical efficacy. Additional characterization assays which compared the ability to neutralize other activities mediated by soluble TNFα (both NFκB-dependent and NFκB-independent), or assays which compared binding kinetics for soluble TNFα or transmembrane TNFα, were also included in the functional similarity assessment.

In addition to testing the primary mechanism of action, binding to FcγRIIIa and induction of ADCC and CDC were tested in sensitive assays. ADCC and CDC are mediated by the Fc region of the antibody and can be affected by differences in specific glycans, which are sensitive to the cell line and manufacturing process. Results from these assays were assessed using Tier 2 criteria, reflective of their potential contribution to clinical efficacy and safety, particularly in the inflammatory bowel disease indications. Binding to FcRn, which could affect the clearance of the product, was also assessed using Tier 2 criteria.

Additional characterization assays were performed to further evaluate the functional similarity of ABP 501 and adalimumab (without statistical criteria). These characterization assays included:

- methods orthogonal to other assays such as complement component 1,q (C1q) binding (orthogonal to CDC) or FcγRIIIa (158F) binding (orthogonal to FcγRIIIa [158V])
- the inhibition of proliferation in a mixed lymphocyte reaction
- activities which are not critical to clinical efficacy or safety such as binding to FcγRIa and FcγRIIa

The full list of methods used to establish the functional similarity of ABP 501 compared to adalimumab is provided in Table 5. Not all of the assay results from the functional similarity assessment are presented in this document, although they were included in the biologics license application. The results from the similarity testing in selected key assays are presented in the following sections, while information on the specific assay methods is provided in Appendix 1.

## Table 5. Summary of all Functional Similarity Assays

| Assay | Tier - Similarity Assessment Approach | Demonstrated Similarity |
|---|---|---|
| Apoptosis inhibition bioassay | 1 – Equivalence acceptance criterion | √ |
| Soluble TNFα binding | 1 – Equivalence acceptance criterion | √ |
| Binding kinetics to soluble TNFα | 3 - Qualitative comparison | √ |
| Binding to transmembrane TNFα | 3 - Qualitative comparison | √ |
| Inhibition of soluble TNFα-induced IL-8 in HUVEC | 3 - Qualitative comparison | √ |
| Inhibition of soluble TNFα-induced cell death in L929 cells | 3 - Qualitative comparison | √ |
| Inhibition of soluble TNFα induced chemokines ex vivo | 3 - Qualitative comparison | √ |
| Specificity against LTα in a HUVEC assay | 3 - Qualitative comparison | √ |
| FcγRIIIa (158V) binding | 2 - Quality range | √ |
| FcγRIIIa (158V) + TNFα binding | 3 - Qualitative comparison | √ |
| FcγRIa binding | 3 - Qualitative comparison | √ |
| FcγRIIa (131H) binding | 3 - Qualitative comparison | √ |
| FcγRIIIa (158F) binding | 3 - Qualitative comparison | √ |
| C1q binding | 3 - Qualitative comparison | √ |
| FcRn binding | 2 - Quality range | √ |
| Induction of ADCC | 2 - Quality range | √ |
| Induction of CDC | 2 - Quality range | √ |
| Inhibition of proliferation in an MLR | 3 - Qualitative comparison | √ |

ADCC = antibody-dependent cell-mediated cytotoxicity; C1q = complement component 1,q; CDC = complement-dependent cytotoxicity; F = phenylalanine; Fab = fragment antigen binding; Fc = fragment crystallizable; FcγRIa = Fc gamma receptor type Ia; FcγRIIa = Fc gamma receptor type IIa; FcγRIIIa = Fc gamma receptor type IIIa; FcRn = neonatal Fc receptor; H = histidine; HUVEC =human umbilical vein endothelial cells; IL-8 = interleukin-8; LTα = lymphotoxin alpha; MLR = mixed lymphocyte reaction; soluble TNFα = soluble tumor necrosis factor alpha; V = valine.

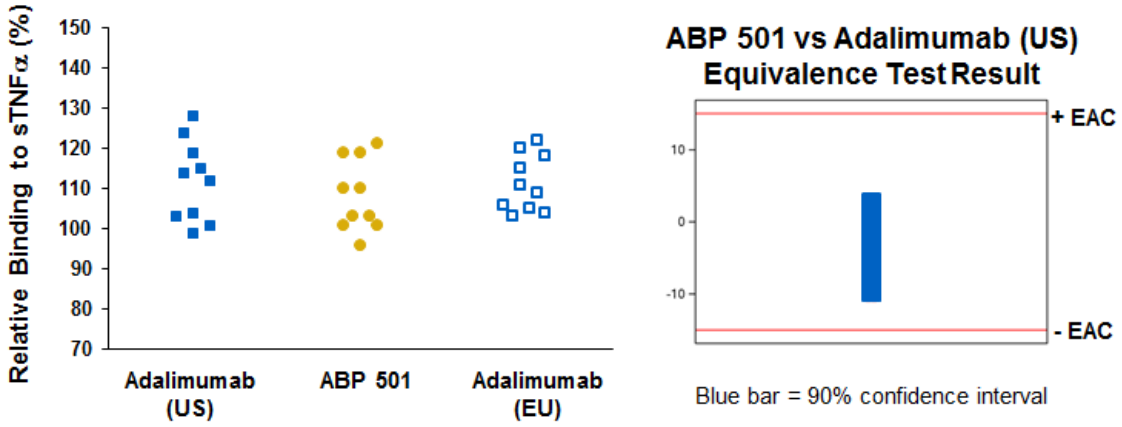
### 3.2.2.1 Assessment of Fab-mediated Activities

**Binding to Soluble TNFα**

The primary mechanism of action of ABP 501 and adalimumab is binding to soluble TNFα, which prevents TNFα binding to TNFα receptors and downstream signaling events (Section 2.2). Since binding and neutralization of soluble TNFα is the primary mechanism of action in all indications for which ABP 501 licensure is being sought (Table 3), the results are critical when considering the totality of evidence for similarity and for extrapolation to indications not studied during the ABP 501 clinical program.

Similarity in binding to soluble TNFα was assessed using an enzyme-linked immunosorbent assay (ELISA), and the results for ABP 501 and adalimumab are presented in Figure 17. Additionally, a graph showing the confidence interval in relation to the adalimumab (US) derived Tier 1 equivalence acceptance criterion (EAC), as described in Section 3.1, is provided. The 90% confidence interval for the difference in means falls within the EAC, and therefore, the soluble TNFα binding of ABP 501 and adalimumab (US) are statistically equivalent.

**Figure 17. Relative Binding to Soluble TNFα**




EAC = equivalence acceptance criterion; sTNFα = soluble tuor necrosis factor alpha.

The relative binding is determined by assessing dose response relative to a reference standard. Each point in the plot represents the result for a unique lot of the indicated product.

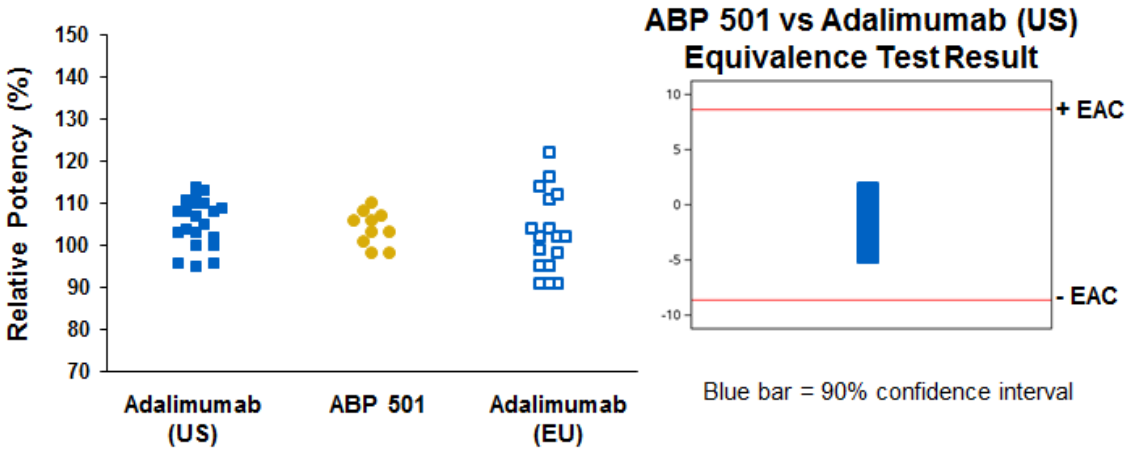
**Apoptosis Inhibition Bioassay**

The apoptosis inhibition bioassay is a cell-based assay that measures a biological outcome of soluble TNFα neutralization and is representative of the primary mechanism of action. The assay measures the ability of ABP 501 or adalimumab to inhibit soluble TNFα induced apoptosis of the human monocyte cell line, U-937, an NFκB-independent function. Amgen has measured functional neutralization of soluble TNFα using both

NFκB dependent and independent methods (Table 5), of which the apoptosis inhibition bioassay is considered the most robust. Additionally, since neutralization of soluble TNFα activity is the primary mechanism of action in all indications for which ABP 501 licensure is being sought, the results are critical in evaluating the totality of evidence for similarity and for the justification of extrapolation to indications not studied during the ABP 501 clinical program.

The apoptosis inhibition results for ABP 501 and adalimumab are presented in Figure 18. Additionally, a graph showing the confidence interval in relation to the adalimumab (US) established Tier 1 EAC is provided. The 90% confidence interval for the difference in means falls within the EAC. Therefore, the apoptosis inhibition of ABP 501 and adalimumab (US) are statistically equivalent, and the products are concluded to have similar apoptosis inhibitory activities.

**Figure 18. Relative Apoptosis Inhibition Results**



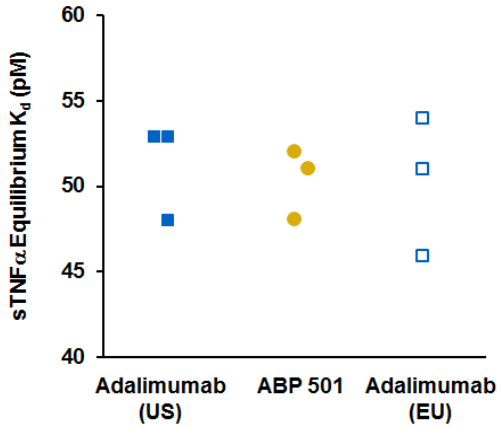

EAC = equivalence acceptance criterion.

The relative potency (%) is determined by assessing dose response relative to a reference standard. Each point in the plot represents the result for a unique lot of the indicated product.

### Soluble TNFα Binding Kinetics by Surface Plasmon Resonance

To further characterize the similarity of binding, surface plasmon resonance (Biacore) analysis was used to determine the association and dissociation rate constants and dissociation equilibrium binding constant ($K_d$) for soluble TNFα binding by ABP 501 and adalimumab. This measurement further examines similarity in soluble TNFα binding as determined in the ELISA shown above. A representative set of 3 lots each of ABP 501, adalimumab (US), and adalimumab (EU) were tested. ABP 501 and adalimumab demonstrated similar soluble TNFα binding kinetics, as represented in the resulting binding constants ($K_d$) (Figure 19).

**Figure 19. Comparison of Binding Kinetics to Soluble TNFα**




$K_d$ = dissociation equilibrium binding constant; sTNFα =soluble tumor necrosis factor alpha.

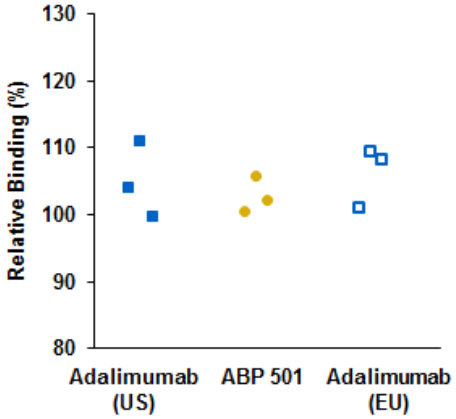
The $K_d$ is determined by surface plamon resonance. Each point in the plot represents the result for a unique lot of the indicated product.

### Binding to Transmembrane TNFα

Adalimumab is known to bind transmembrane TNFα, and reduction in the number of transmembrane TNFα-expressing cells may be relevant to efficacy in inflammatory bowel diseases (discussed in more detail in Section 2.2). Because binding to transmembrane TNFα is a plausible mechanism of action (Table 3), ABP 501 and adalimumab were further characterized for binding to transmembrane TNFα. The binding results contribute to the totality of evidence for analytical similarity and to the justification of extrapolation to all the indications in which Amgen is seeking licensure.

ABP 501 and adalimumab were tested for transmembrane TNFα binding in a competitive binding cell-based assay. This measurement complements the assessment of soluble TNFα binding (Figure 17), since the binding epitope recognized by adalimumab is the same for both soluble TNFα and transmembrane TNFα (Hu et al, 2013). Therefore, a representative set of 3 lots each of ABP 501, adalimumab (US), and adalimumab (EU) were tested. ABP 501 demonstrated highly similar transmembrane TNFα binding compared to adalimumab (Figure 20).

**Figure 20. Comparison of Transmembrane TNFα Binding**



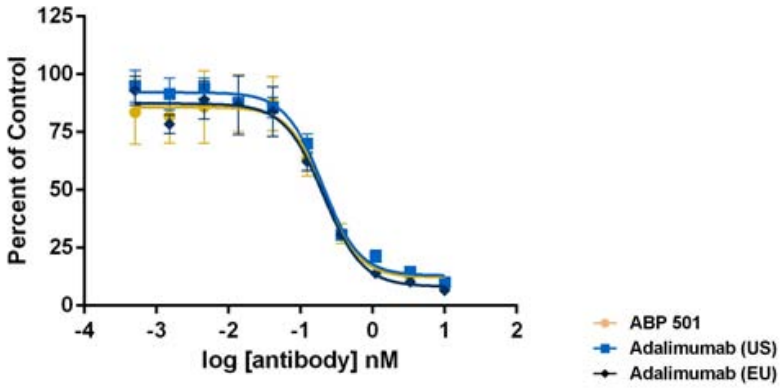

TNFα = tumor necrosis factor alpha.

The relative binding (%) is determined by assessing dose response relative to a reference standard. Each point in the plot represents the result for a unique lot of the indicated product.

### TNFα-induced Cytokine Production in Endothelial Cells

TNFα can induce inflammatory signaling in endothelial cells, an NFκB-dependent activity. An assay to monitor NFκB-dependent, TNFα-induced IL-8 secretion in human umbilical vein endothelial cells (HUVEC) was developed as an additional, orthogonal characterization assay. Since this assay further characterizes similarity in neutralization of soluble TNFα activity (Figure 18), a representative set of 3 lots each of ABP 501, adalimumab (US), and adalimumab (EU) were tested. ABP 501 and adalimumab had similar potency in neutralizing the activity of soluble TNFα in this NFκB-dependent pathway (Figure 21).

**Figure 21. Representative Data Comparing Inhibition of Soluble TNFα-induced Interleukin-8 in HUVEC**




HUVEC = human umbilical vein endothelial cells; TNFα = tumor necrosis factor alpha.

Each point is the mean derived from 3 within assay replicates ± standard error of the mean.

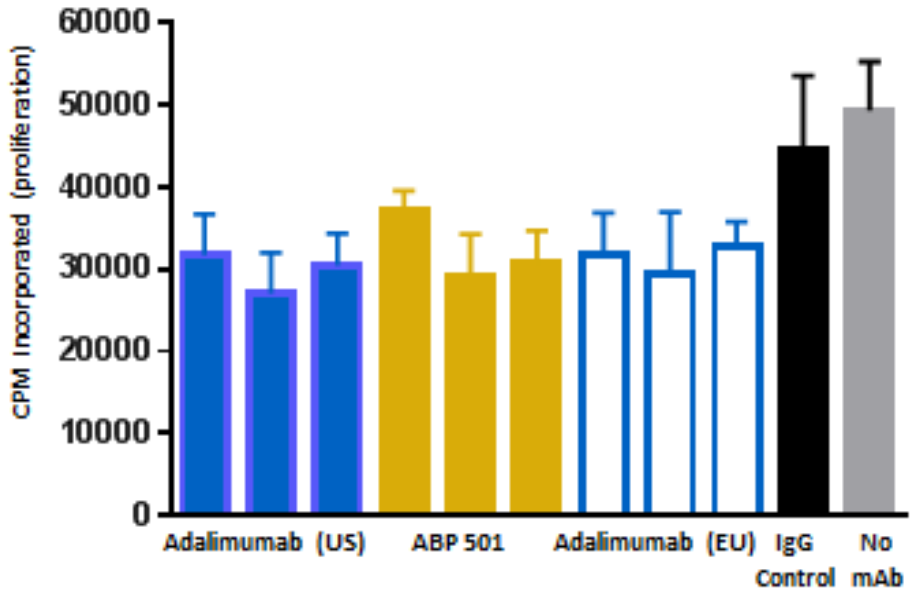
#### 3.2.2.2 Assessment of Fab- and Fc-mediated Activities

**Transmembrane TNFα Binding Functional Assay: Inhibition of Proliferation in a Mixed Lymphocyte Reaction**

Literature suggests that the dual activity of the Fab and Fc regions are required for adalimumab mediated inhibition of T cell proliferation in vitro. Inhibition of T cell proliferation in a mixed lymphocyte reaction has been proposed to be mediated by the induction of regulatory macrophages through engagement of transmembrane TNFα on activated T cells and Fc receptors on macrophages. Since binding to transmembrane TNFα is a potential mechanism of action in the inflammatory bowel disease indications for which ABP 501 licensure is being sought (Table 3), the results are particularly relevant to the justification for extrapolation.

The mixed lymphocyte reaction assay is performed with primary cells from 2 different donors. The proliferation of cells in the assay in response to “non-self” signals can be quite variable across donor pairs, and as a result, the mixed lymphocyte reaction assay has a relatively small signal window. Thus, the assay is conducted with a single concentration of antibody, and a qualitative assessment of similarity is performed. The results from the test antibody are compared to the level of proliferation observed in the presence of the same concentration of an isotype matched control antibody (ie, an antibody that does not bind TNFα) or in the absence of any antibody. A representative set of 3 lots each of ABP 501, adalimumab (US), and adalimumab (EU) were tested. ABP 501 and adalimumab demonstrated similar inhibition of cellular proliferation in the mixed lymphocyte reaction (Figure 22), with proliferation in the presence of ABP 501 or adalimumab lower than that observed in the presence of an IgG1 control antibody without TNF inhibitory activity or in the absence of any antibody.

**Figure 22. Inhibition of Proliferation in a Mixed Lymphocyte Reaction**




CPM = counts per minute, a direct measure of proliferation; IgG = immunoglobulin isotype G; mAb = monoclonal antibody.

Each bar represents the mean ± standard deviation from 5 within assay replicates for 3 unique lots of adalimumab and ABP 501; 5 replicates are represented for the IgG and no ant body controls.

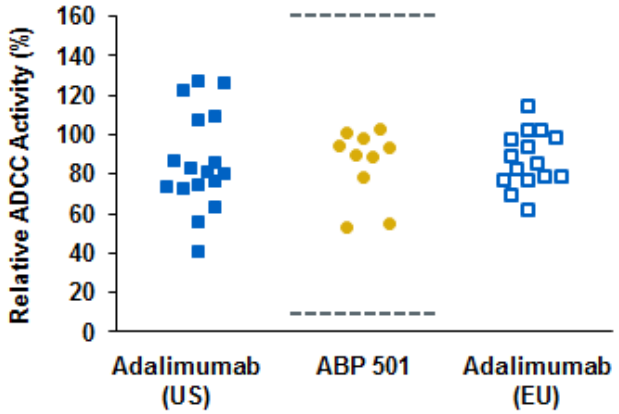
### Antibody-dependent Cell-mediated Cytotoxicity (ADCC)

ADCC occurs when antibodies bind to antigens expressed on target cells and the antibody Fc region engages Fc receptors (eg, FcγRIIIa) on the surface of immune effector cells. This leads to the activation of the effector cell, release of cytolytic granules, and target cell death mediated by the cytolytic proteins present within the released granules. For adalimumab and ABP 501, ADCC requires binding to transmembrane TNFα and to FcγRIIIa. The latter is highly sensitive to the glycan structure of the antibody, an attribute that is influenced by both the cell line and manufacturing process. Therefore, ADCC is an important method to assess the primary and higher order structure of the Fab and Fc regions and the effect of variations in key glycan structures. Therefore, all 10 ABP 501 lots were tested, and the results were assessed using Tier 2 criteria (Section 2.2). Additionally, since ADCC is a potential mechanism of action in the inflammatory bowel disease indications for which ABP 501 licensure is being sought (Table 3), the results contribute to the totality of evidence supporting the justification of extrapolation to the indications that were not studied in the ABP 501 clinical program.

ABP 501 had similar ADCC activity compared to adalimumab (Figure 23). All ABP 501 lots were within the adalimumab (US) Tier 2 quality range. Therefore, ABP 501 is

considered similar to adalimumab for ADCC activity. These results confirm that the minor differences observed in the glycan profile (Section 3.2) did not affect similarity in ADCC activity.

**Figure 23. Relative ADCC Activity Results**




ADCC = antibody-dependent cellular cytotoxicity.

The relative activity (%) is determined by assessing ADCC activity relative to a reference standard. Each point in the plot represents the result for a unique lot of the indicated product.

The dotted lines represent the quality range based on adalimumab (US) results.

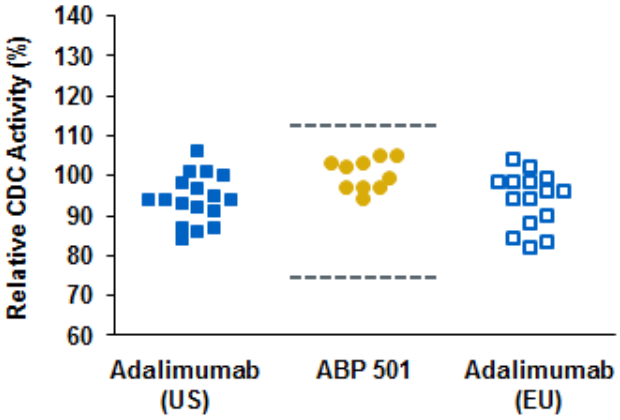
### Complement-dependent Cytotoxicity (CDC)

Similar to ADCC, another mechanism for inducing cell clearance is the induction of CDC. CDC occurs when an antibody binds to an antigen on the surface of a target cell and the Fc region of the antibody activates the complement cascade. The cascade begins with binding to C1q, which initiates the formation of a membrane attack complex, leading to pore formation in the target cell membrane and ultimately to cell lysis. For adalimumab and ABP 501, CDC requires binding to transmembrane TNFα and to C1q, and subsequently to other complement components. The glycan structure of the antibody affects the efficiency of C1q binding. Therefore, CDC is an important orthogonal method to assess the primary and higher order structure of the Fab and Fc regions, and the presence of key glycan structures. Therefore, all 10 ABP 501 lots were tested, and the results were assessed using Tier 2 criteria. Additionally, since CDC is a potential mechanism of action in the inflammatory bowel disease indications for which ABP 501 licensure is being sought (Table 3), the results support the totality of evidence for similarity and the justification of extrapolation to the indications that were not studied in the ABP 501 clinical program.

ABP 501 had similar CDC activity compared to adalimumab (Figure 24). All ABP 501 lots were within the adalimumab (US) Tier 2 quality range. Therefore, ABP 501 is

considered similar to adalimumab for CDC activity. These results confirm that the minor differences observed in the glycan profile (Section 3.2) did not affect similarity in CDC activity.

**Figure 24. Relative CDC Activity Results**




CDC = complement-dependent cytotoxicity.

The relative activity (%) is determined by assessing CDC activity relative to a reference standard. Each point in the plot represents the result for a unique lot of the indicated product.

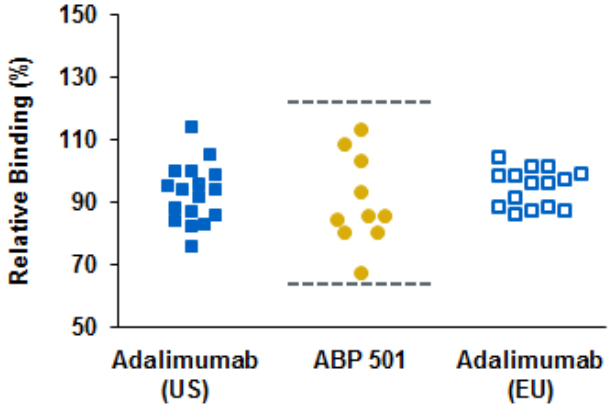
The dotted lines represent the quality range based on adalimumab (US) results.

### 3.2.2.3 Assessment of Fc-mediated Binding Activities

**FcγRIIIa (158V) binding**

FcγRIIIa is a pro-inflammatory receptor expressed on human natural killer cells and is involved in the induction of ADCC. FcγRIIIa binding, as mentioned previously, is highly sensitive to the glycan structure of the antibody. Therefore, FcγRIIIa binding is an important method to assess the primary and higher order structure of the Fc region in addition to the presence of key glycan structures (Section 2.2). A genetic polymorphism in FcγRIIIa results in expression of either valine (V) or phenylalanine (F) at amino acid 158. The 2 isoforms differ in their affinity for IgG1, with the 158V isoform having the highest affinity. A competitive AlphaLISA™ binding assay was developed to assess the binding of ABP 501 and adalimumab to FcγRIIIa (158V). ABP 501 and adalimumab are similar with respect to FcγRIIIa (158V) binding, as presented in Figure 25. FcγRIIIa (158F) binding was also tested and shown to be similar.

**Figure 25. Relative Binding to FcγRIIIa (158V)**




FcγRIIIa = Fc-gamma receptor type IIIa; V = valine.

The relative binding (%) is determined by assessing FcγRIIIa (158V) binding relative to a reference standard. Each point in the plot represents the result for a unique lot of the indicated product.

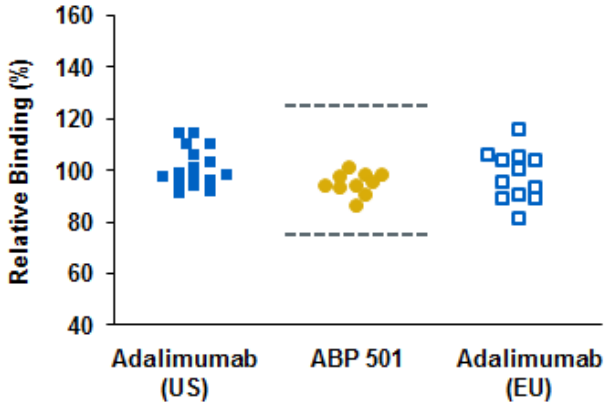
The dotted lines represent the quality range based on adalimumab (US) results.

### Binding to FcRn

FcRn binds to the Fc region of IgG under mildly acidic conditions (~ pH 6) found in the endosome and recycles IgG back into the serum. In the absence of FcRn, antibodies are degraded in the lysosomal compartment of cells that mediate clearance. Thus, FcRn contributes to IgG homeostasis in humans by maintaining serum IgG levels, and differences in FcRn binding can affect the PK profile of a therapeutic antibody. Consequently, FcRn binding is an important contribution to the assessment of analytical similarity as an orthogonal method to assess the primary and higher order structure of the Fc region.

ABP 501 had similar FcRn binding activity compared to adalimumab (Figure 26). All ABP 501 lots are within the adalimumab (US) Tier 2 quality range. Therefore, ABP 501 is similar to adalimumab for FcRn binding activity.

**Figure 26. Relative Binding to FcRn**




FcRn = fragment crystallizable neonatal receptor.

The relative binding (%) is determined by assessing FcRn binding relative to a reference standard. Each point in the plot represents the result for a unique lot of the indicated product.

The dotted lines represent the quality range based on adalimumab (US) results.

### 3.3 Analytical Similarity Conclusion

The comprehensive analytical similarity assessment demonstrates that ABP 501 is highly analytically similar to adalimumab. Some minor analytical differences in structural and purity attributes were observed between ABP 501 and adalimumab, but based on adalimumab product knowledge these were not expected to affect the functional activities or PK of ABP 501. The minor differences were confirmed to have no effect on the functional activities through extensive analytical testing that determined the functional similarity between ABP 501 and adalimumab and, notably, assessed all known and plausible mechanisms of action for adalimumab. Importantly, the Tier 1 attributes were demonstrated to be similar within the pre-specified assessment criteria. Furthermore, the minor structural differences were confirmed to have no effect on efficacy, safety, or immunogenicity in the ABP 501 clinical studies (Section 5).

#### 3.3.1 Similarity in All Mechanisms of Action Supports Extrapolation in All Indications

TNFα can induce cytokine and chemokine production, adhesion molecule expression, proliferation, angiogenesis, and apoptosis through the soluble version of the cytokine engaging TNFR1 and signaling through multiple downstream pathways. These molecular events are central to the propagation of autoimmune disease pathology as depicted in Figure 14 and Figure 16. The functional similarity data presented in this section demonstrate that ABP 501 is highly similar to adalimumab in inhibiting soluble TNFα signaling, including both the NFκB-dependent and NFκB-independent pathways (Table 3).

Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, juvenile idiopathic arthritis, and plaque psoriasis share common molecular mechanisms of TNF-dependent disease pathologies, based on prescribing information for adalimumab, published studies, and knowledge gained from testing various TNFα inhibitors clinically. Thus, the analytical similarity of ABP 501 to adalimumab, along with the clinical study results in rheumatoid arthritis and plaque psoriasis (discussed in Section 5) support the use of ABP 501 in these indications.

As reviewed in Section 2.2, it is known from published literature that pro-inflammatory soluble TNFα signaling also drives inflammation in inflammatory bowel disease, but that additional, less well-understood mechanisms of action through the modulation of transmembrane TNFα may also contribute to efficacy in those indications. The similarity of ABP 501 to adalimumab has been demonstrated in an extensive functional characterization assessment that included multiple assays assessing these secondary mechanisms of action (Table 3). The results of these assessments, when considered with the results of the overall analytical similarity assessment and the similarity in clinical PK, safety, and efficacy in both the rheumatoid arthritis and plaque psoriasis clinical studies, support the approval of ABP 501 as a biosimilar to adalimumab. Additionally, the results support extrapolation to all of the indications not studied in the ABP 501 clinical program.

# 4. NONCLINICAL DEVELOPMENT PROGRAM

A nonclinical program was designed to assess the toxicologic characteristics of ABP 501 as part of the stepwise assessment of similarity. A 1-month comparative toxicology study in the cynomolgus monkey (Study 115674) was conducted to compare toxicities of ABP 501 and adalimumab, and to demonstrate a lack of unexpected toxicities with ABP 501 administration. Additionally, the toxicokinetic profiles of ABP 501 and adalimumab were assessed.

## 4.1 Nonclinical Background

Amgen conducted a review of the publicly available nonclinical safety assessments of adalimumab. The cynomolgus monkey is considered a pharmacologically relevant species for ABP 501 and adalimumab since ABP 501 and adalimumab can bind cynomolgus monkey TNFα and neutralize its biological activity. Although there are no pharmacodynamic markers that are sensitive and specific for anti-TNFα agents in healthy animals, there are expected drug effects that can be observed after high dose adalimumab treatment in monkeys (European Public Assessment Report, 2006; FDA Approval Package for Humira, Pharmacology Review, 2002). Thus, a comparative monkey toxicology study, including splenic B cell type and number using flow cytometry and immunohistochemistry, was chosen.

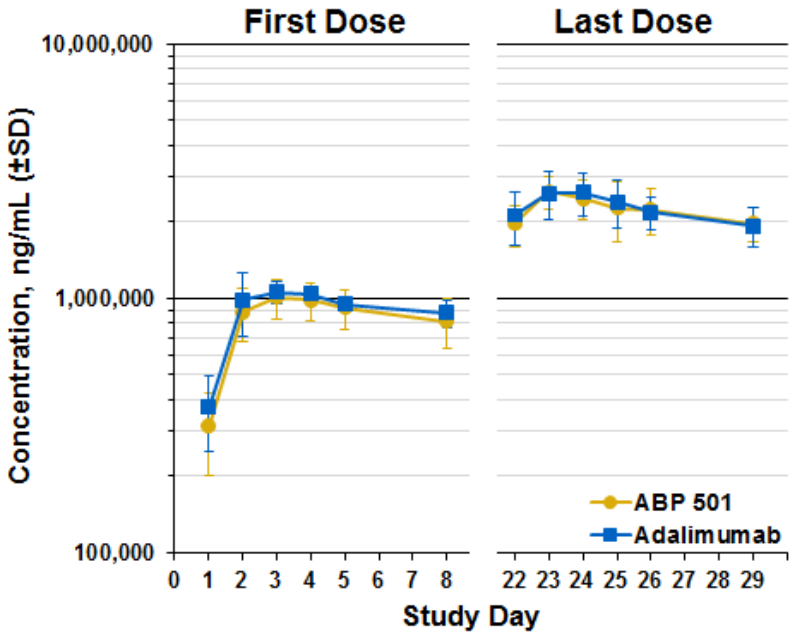
## 4.2 Species, Dose, Regimen, and Duration for the Comparative Toxicology Study

The species, dose, regimen, and duration for the comparative toxicology study were selected to provide a meaningful toxicological comparison of ABP 501 and adalimumab (US). Selection of the dose and duration for the 1-month study was based on adalimumab literature to evaluate the expected effects on lymphoid cells and to identify potential differences in toxicological effects (European Public Assessment Report, 2006; FDA Approval Package for Humira, Pharmacology Review, 2002). Subcutaneous administration was the route of administration used in the toxicology study because ABP 501 is administered subcutaneously in the clinic.

## 4.3 Comparative Toxicology Study 115674

Study 115674 compared 157 mg/kg/week doses of ABP 501 and adalimumab. The study demonstrated similar toxicokinetic parameters after single and repeat dosing (Figure 27), confirming that male and female cynomolgus monkeys treated with ABP 501 and adalimumab experienced similar exposure.

**Figure 27. Toxicokinetic Profile for ABP 501 and Adalimumab in Cynomolgus Monkeys After Single and Repeat Dosing in Study 115674**




SD = standard deviation.

ABP 501 and adalimumab were well tolerated and no unexpected toxicity was observed. The expected lymphoid changes for ABP 501 and adalimumab were similar. Decreased size and number of germinal centers in axillary lymph nodes, mesenteric lymph nodes, and tonsil characterized the lymphoid changes. In the spleen, immunohistochemical staining and flow cytometry showed decreased CD21+ B lymphocytes. The lymphoid findings were consistent with those observed following adalimumab treatment of monkeys in historical studies (European Public Assessment Report, 2006; FDA Approval Package for Humira, Pharmacology Review, 2002). Effects at the injection site were considered secondary to the injection procedure. The difference in formulation (Section 2.3) between ABP 501 and adalimumab did not affect the toxicity or toxicokinetic profile of ABP 501. The nonclinical study comparing ABP 501 and adalimumab did not identify any new toxicologic findings.

## 4.4 Key Conclusions of the Nonclinical Program

ABP 501 and adalimumab had similar toxicokinetics and both induced the expected lymphoid changes in the cynomolgus monkey Study 115674, with no unexpected toxicities observed. The nonclinical toxicokinetics and nonclinical safety data, when assessed with the totality of evidence, support the conclusion that ABP 501 is highly similar to adalimumab.

## 5. CLINICAL

To demonstrate the similar PK, efficacy, safety, and immunogenicity of ABP 501 to adalimumab, Amgen designed and conducted a comprehensive biosimilar clinical program. The program consisted of studies in sensitive populations, ie, populations in whom potential differences between ABP 501 and adalimumab are likely to be detected, if such differences exist. The studies used clinically relevant and sensitive endpoints to evaluate similarity. This section describes the study designs and the results of the clinical program. When considered with the highly similar analytical and nonclinical results, the clinical program completes the totality of evidence. The results support the approval of ABP 501 as a biosimilar to adalimumab in all indications for which Amgen seeks ABP 501 licensure.

### 5.1 Overview

The clinical evidence supporting the similarity of ABP 501 to adalimumab includes the following studies:

- a single-dose, PK similarity study
  - Study 20110217 in healthy subjects
- 2 randomized, double-blind, active comparator-controlled studies
  - Study 20120262 in subjects with moderately to severely active rheumatoid arthritis
  - Study 20120263 in subjects with moderate to severe chronic plaque psoriasis

Additionally, a single-arm, open-label extension study from Study 20120262 in subjects with rheumatoid arthritis was completed in June 2016 (Study 20130258), and the data are currently being analyzed.

Key features for each clinical trial are shown in Table 6.

**Table 6. ABP 501 Clinical Studies**

| Study Number | Subject Population | Type of Study | Number of Subjects | Study Duration | Primary Endpoint(s) |
|---|---|---|---|---|---|
| 20110217 | Healthy subjects | PK similarity | 203 | 63 days | $AUC_{inf}$ and $C_{max}$ |
| 20120262 | Rheumatoid arthritis | Efficacy, safety, and immunogenicity | 526 | 26 weeks | ACR20 at week 24 |
| 20130258 | | Long-term safety, immunogenicity, and efficacy | 467 | 72 weeks | Safety, ACR20, DAS28-CRP |
| 20120263 | Plaque psoriasis | Efficacy, safety, and immunogenicity | 350 | 52 weeks | PASI percent improvement from baseline at week 16 |

ACR20 = 20% improvement in American College of Rheumatology; $AUC_{inf}$ = area under the concentration time curve from time 0 to infinity; $C_{max}$ = maximum observed drug concentration during a dosing interval; Disease Activity Score 28 C-reactive protein; PASI = Psoriasis Area and Severity Index; PK = pharmacokinetic.

For Study 20110217, healthy subjects were selected to assess PK similarity since these subjects do not receive concomitant medications and do not have medical conditions that could potentially affect PK. The approved dose of adalimumab in most adult indications is 40 mg, and therefore a 40 mg dose was selected for the study. The study demonstrated PK similarity between ABP 501 and adalimumab (US), as well as PK similarity between ABP 501 and adalimumab (EU) and between adalimumab (US) and adalimumab (EU).

Adalimumab (US) and adalimumab (EU) PK similarity results, along with data from analytical similarity studies, were used to establish the scientific bridge for the adalimumab sourced from the 2 different regions. Therefore, the single-sourced comparators used in Study 20120262 (adalimumab [US]) and in Study 20120263 (adalimumab [EU]) both provide relevant clinical similarity information to assess biosimilarity.

Subjects with moderately to severely active rheumatoid arthritis on concomitant methotrexate represent an appropriate population to evaluate clinical similarity in terms of efficacy, safety, and immunogenicity. Additionally, this population is representative of other approved adalimumab indications and thus supports extrapolation. In the rheumatoid arthritis Study 20120262, the primary efficacy endpoint of ACR20 at week 24 was selected to assess similarity in efficacy. This is because of its historical use in all regulatory assessments for adalimumab approval and a demonstrated large effect size over placebo. Therefore, ACR20 is a sensitive measure of clinically meaningful benefit

and potential difference in treatments. The 90% confidence interval was used to ensure that the study-wise type I error was controlled at the 0.05 level. The margin was selected based on review of a meta-analysis of historical adalimumab clinical trials.

Study 20120263 in subjects with moderate to severe chronic plaque psoriasis studied a relatively younger population with fewer comorbidities and concomitant medications, thus a sensitive population. As such, this population is appropriate to demonstrate clinically meaningful differences in efficacy, safety, and immunogenicity between ABP 501 and adalimumab, if such differences exist. Additionally, this population is representative of other approved adalimumab indications and therefore supports extrapolation. The primary endpoint of PASI percent improvement from baseline is a continuous variable retaining full information of the assessment and therefore a sensitive and appropriate endpoint to evaluate the clinical similarity of ABP 501 and adalimumab. Study 20120263 also included an assessment of efficacy, safety, and immunogenicity in a subset of subjects who underwent a single transition from adalimumab to ABP 501 at week 16 in comparison with those subjects who continued their initial treatment on adalimumab. The 95% confidence interval was used to ensure that the study-wise type I error was controlled at the 0.025 level per advice from the European Medicines Agency (Section 5.3.2).

The clinical study in subjects with moderately to severely active rheumatoid arthritis (Study 20120262) demonstrated the clinical similarity in safety, efficacy, and immunogenicity for ABP 501 and adalimumab in the primary efficacy analysis of ACR20 at week 24. The 90% confidence interval for risk ratio of ACR20 between ABP 501 and adalimumab was fully contained within the pre-defined equivalence margin (0.738, 1/0.738 [ie, 1.355]) (Section 5.3.1). Thus, the successful demonstration of clinical equivalence in efficacy between ABP 501 and adalimumab supports the demonstration of biosimilarity and the extrapolation to other conditions of use for which Amgen is seeking ABP 501 licensure.

Study 20120263 demonstrated the clinical equivalence of ABP 501 and adalimumab in the primary efficacy analysis of PASI percent improvement from baseline at week 16, with the 95% confidence interval for the treatment difference fully contained within the pre-defined equivalence margin of ± 15%. Thus, the successful demonstration of clinical equivalence in efficacy between ABP 501 and adalimumab supports a conclusion of biosimilarity and the extrapolation to other conditions of use for which Amgen is seeking ABP 501 licensure. The study also found that there is no increased risk with respect to

safety, efficacy, or immunogenicity associated with the single transition from adalimumab to ABP 501.

In both Study 20120262 and Study 20120263 the primary analysis of the primary endpoint was conducted using the last observation carried forward method since it is appropriate and conservative when assessing equivalence. All secondary endpoints and sensitivity analyses using different analysis populations and imputation methods were consistent with the findings of the primary efficacy analyses. None of the studies showed clinically meaningful differences in the safety profiles, which were consistent with the known adalimumab profile, and no new safety signals were observed. Binding and neutralizing antibody development was also similar (see Section 5.4 for results).

The totality of the evidence supports that ABP 501 is highly similar to the reference product notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences in terms of efficacy, safety, and immunogenicity as compared to adalimumab.

## 5.2 Clinical Pharmacology

The clinical pharmacology program for ABP 501 was designed to assess PK similarity, as evaluated in a single-dose, parallel group Study 20110217 that compared ABP 501 and adalimumab in healthy subjects. The study evaluated the PK similarity between ABP 501 and adalimumab (US), between ABP 501 and adalimumab (EU), and between adalimumab (US) and adalimumab (EU). As described in the clinical overview, healthy subjects are an appropriate population and sensitive to assess PK similarity between ABP 501 and adalimumab.

Factors that may potentially influence adalimumab PK, such as the presence of anti-drug antibodies, concomitant medications (ie, methotrexate), patient demographics (age, gender, and weight), disease variables (ie, C-reactive protein), and disease types (eg, rheumatoid arthritis, ulcerative colitis, Crohn's disease, juvenile idiopathic arthritis, and pediatric Crohn's disease patients) have been examined previously (Humira Summary of Product Characteristics, 2016; Sharma et al, 2015; Humira European Public Assessment Reports, 2007, 2008, 2012). Of the factors investigated, the presence of anti-drug antibodies, concomitant use of methotrexate, body weight, and serum albumin levels could significantly affect adalimumab PK. Different disease clearance mechanisms may potentially exist (Ungar et al, 2016; Brandse et al, 2015; Ternant et al, 2015; Paul et al, 2014; Ternant et al, 2014; Ordas et al, 2012), however, given the demonstrated high

degree of analytical similarity between ABP 501 and adalimumab, it is expected that no clearance difference between the products would occur.

To provide further evidence of the exposure similarity across indications, serial trough PK samples following ABP 501 and adalimumab administration were collected from the clinical studies in subjects with moderately to severely active rheumatoid arthritis (Study 20120262, concomitant methotrexate use) and in subjects with moderate to severe chronic plaque psoriasis (Study 20120263, no methotrexate).

Collectively, the PK similarity of ABP 501 to adalimumab was demonstrated in healthy subjects and in subjects with rheumatoid arthritis and plaque psoriasis.

### 5.2.1 PK Similarity Study 20110217 in Healthy Subjects

#### 5.2.1.1 Study Design

Study 20110217 was a single-blind, single-dose, 3-arm parallel group study in healthy adult subjects assessing PK parameters following single 40 mg subcutaneous doses of ABP 501, adalimumab (US), or adalimumab (EU). The study was designed to assess the PK similarity, as assessed by $AUC_{inf}$ and $C_{max}$. The area under the concentration time curve from time 0 to last quantifiable concentration ($AUC_{last}$) was assessed as a secondary endpoint. Standard FDA bioequivalence criteria were used, in which the 90% confidence intervals for the ratio of geometric means for $AUC_{inf}$ and $C_{max}$ must fall entirely within 0.80 and 1.25. Safety, tolerability, and immunogenicity of all 3 treatments were evaluated as secondary objectives.

In total, 203 subjects (87 women and 116 men) received investigational product and were followed up to 63 days:

- 40 mg ABP 501, 67 subjects (66 completed study)
- 40 mg adalimumab (US), 69 subjects (66 completed study)
- 40 mg adalimumab (EU), 67 subjects (64 completed study)

#### 5.2.1.2 Results

The 90% confidence intervals of the geometric least-squares mean ratios for the comparisons of ABP 501 to adalimumab (US) and ABP 501 to adalimumab (EU) for all 3 PK parameters (the primary parameters $AUC_{inf}$ and $C_{max}$, and secondary parameter $AUC_{last}$) were contained within the standard bioequivalence criteria of 0.80 to 1.25, demonstrating PK similarity (Table 7). Additionally, the PK similarity of adalimumab (US) to adalimumab (EU) was demonstrated using the same criteria, thus supporting the similarity of adalimumab sourced from both regions. The calculated PK parameters are

shown in Table 8 and the serum concentrations-time curves are shown in Figure 28.

The adalimumab results are consistent with those observed in the literature.

**Table 7. Study 20110217 Summary of Geometric Least-squares Mean Ratio (90% Confidence Interval, Pharmacokinetic Parameter Population)**

| PK Parameter | ABP 501 vs Adalimumab (US) | ABP 501 vs Adalimumab (EU) | Adalimumab (US) vs Adalimumab (EU) |
|---|---|---|---|
| $C_{max}$ (µg/mL) | 1.04 (0.964, 1.12) | 0.96 (0.889, 1.03) | 0.92 (0.857, 0.994) |
| $AUC_{inf}$ (h*µg/mL) | 1.11 (1.00, 1.24) | 1. 04 (0.935, 1.17) | 0.94 (0.840, 1.04) |
| $AUC_{last}$ (h*µg/mL) | 1.07 (0.964, 1.18) | 0.99 (0.892, 1.10) | 0.93 (0.836, 1.03) |

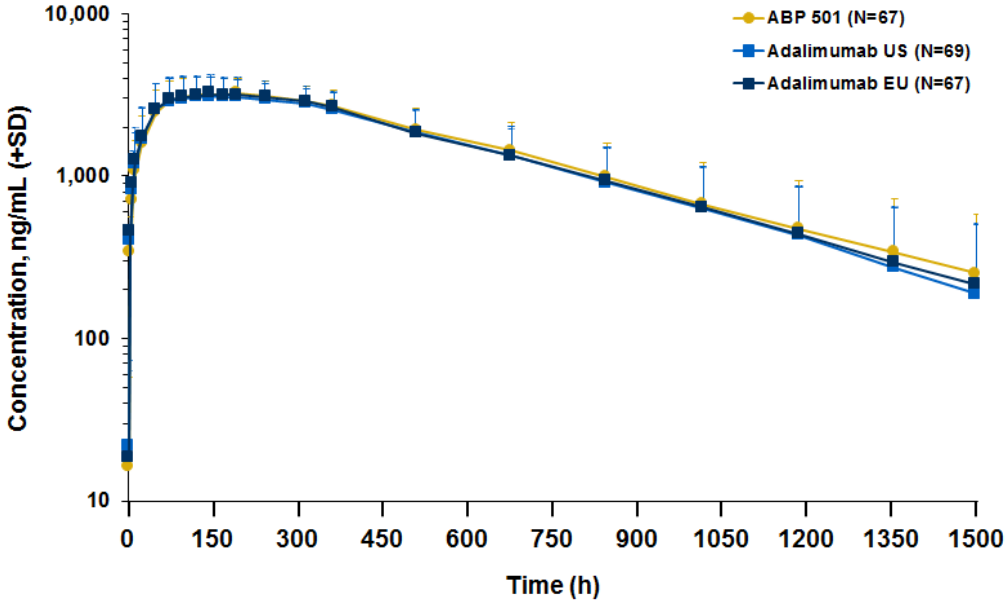
$AUC_{inf}$ = area under the concentration time curve from time 0 to infinity; $AUC_{last}$ = area under the concentration time curve from time 0 to time of last quantifiable concentration; $C_{max}$ = maximum observed concentration; EU = European Union; US = United States.

**Table 8. Study 20110217 Summary of Pharmacokinetics (Geometric Least-squares Means, Pharmacokinetic Parameter Population)**

| PK Parameter | ABP 501 | Adalimumab (US) | Adalimumab (EU) |
|---|---|---|---|
| $C_{max}$ (µg/mL) | 3.22 | 3.11 | 3.37 |
| $AUC_{inf}$ (h* µg/mL) | 2140 | 1920 | 2050 |
| $AUC_{last}$ (h*µg/mL) | 2000 | 1880 | 2020 |

$AUC_{inf}$ = area under the concentration time curve from time 0 to infinity; $AUC_{last}$ = area under the concentration time curve from time 0 to time of last quantifiable concentration; $C_{max}$ = maximum observed concentration; EU = European Union; US = United States.

**Figure 28. Study 20110217 Mean (+SD) Serum Concentration-time Profiles (Pharmacokinetic Parameter Population)**




EU = European Union; SD = standard deviation; US = United States.

### 5.2.2 Comparison and Analyses of PK Results Across Rheumatoid Arthritis and Plaque Psoriasis Studies

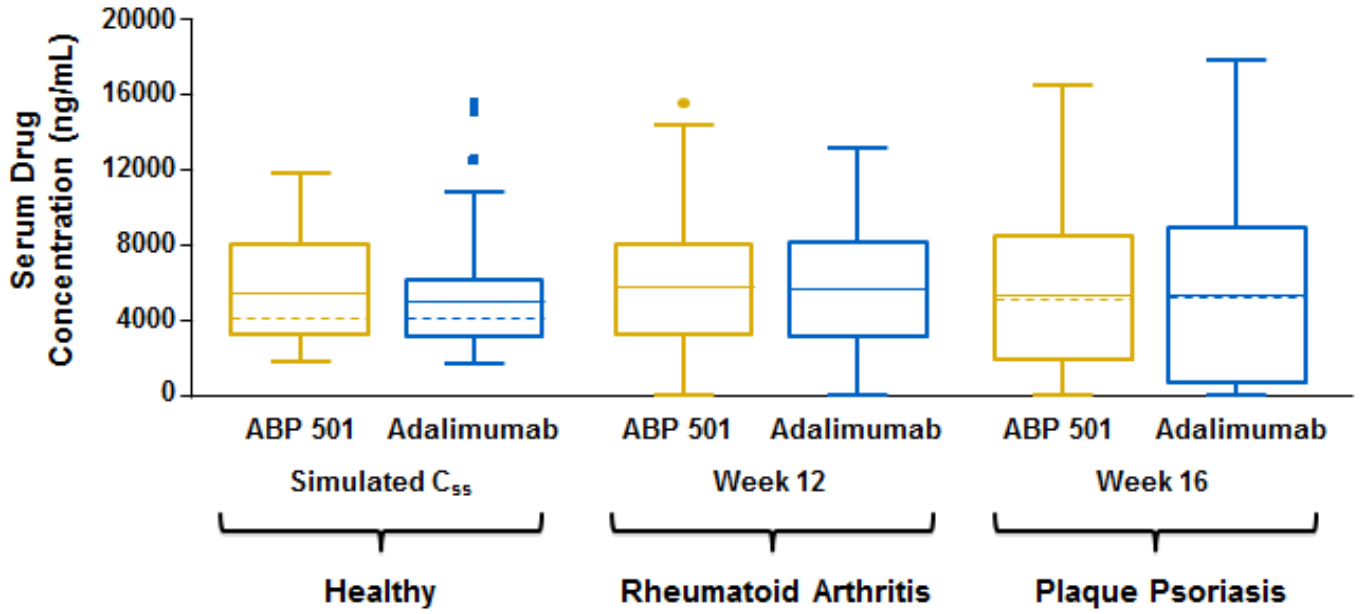
Rheumatoid arthritis Study 20120262 included PK trough sampling summarized descriptively by treatment for each sampling time point over the entire study duration. PK results revealed that trough serum concentrations, the geometric mean, and the geometric coefficient of variation were similar between the ABP 501 and adalimumab groups across study weeks, indicating that study drug exposure was similar between treatment groups.

Study 20120263 in subjects with moderate to severe chronic plaque psoriasis also included PK trough sampling summarized descriptively by treatment for each sampling time point. The PK trough levels observed were similar for ABP 501 and adalimumab over the duration of this study as well (Figure 29).

Simulated trough serum concentrations of ABP 501 and adalimumab in healthy subjects at steady state following 40 mg administered subcutaneously every 2 weeks dosing were estimated for comparison with the corresponding trough serum concentrations observed in Study 20120262 and Study 20120263. The trough concentrations derived from the ABP 501 study in healthy subjects (Study 20110217) are highly consistent with those observed from the ABP 501 studies in rheumatoid arthritis and plaque psoriasis, as well as between ABP 501 and adalimumab, indicating consistency in PK of ABP 501 and similarity with adalimumab across the 3 populations studied (Figure 29).

The overall steady-state trough concentrations and steady-state trough concentrations by anti-drug antibody status remained similar between ABP 501 and adalimumab treated groups (Figure 30). The PK results in sensitive and representative populations indicate that ABP 501 is expected to retain a PK profile similar to adalimumab in all indications, and thus supports extrapolation to all indications of use for which licensure is sought.

**Figure 29. Serum Trough Concentration Comparisons**
**(Study 20110217, Study 20120262, and Study 20120263 Pharmacokinetic Analysis Sets)**

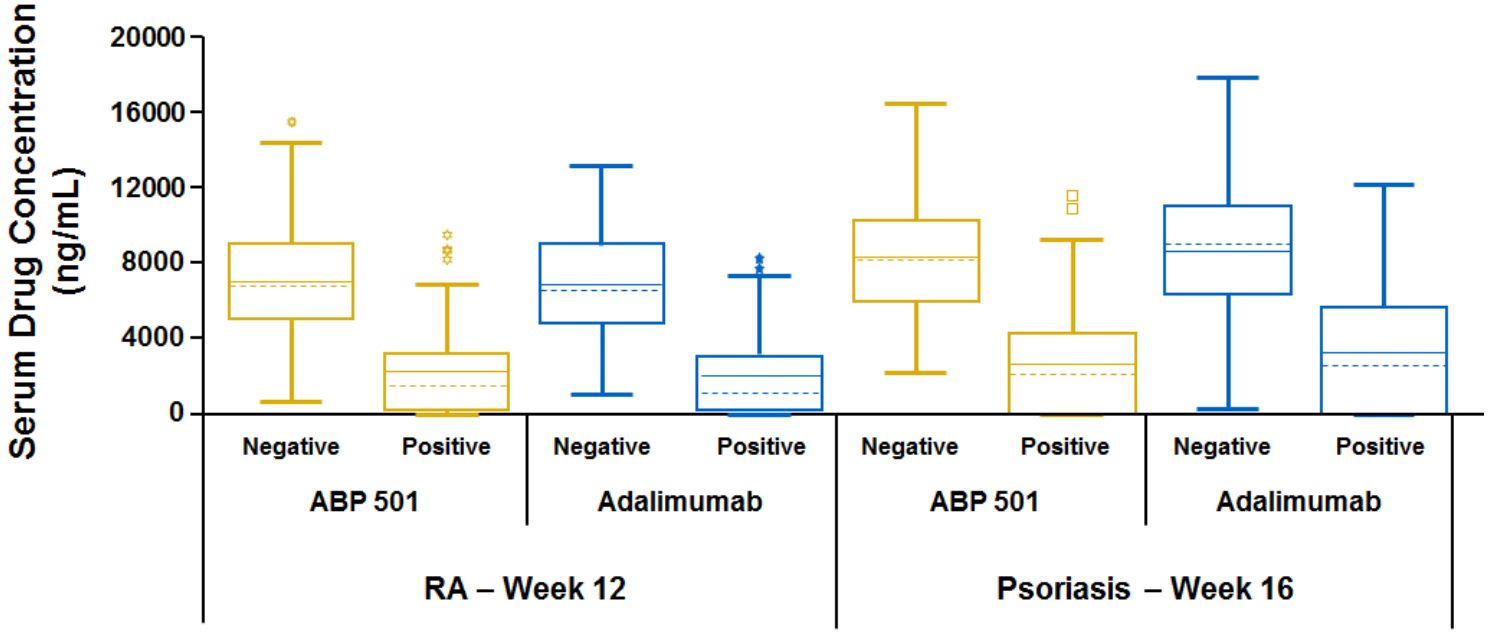



Note: Trough concentrations for subjects in Study 20110217 are projected. Trough at steady state was calculated based on serum concentrations observed at 312 hours and half-life values calculated by noncompartmental PK analysis. The overall formula is as follows: 1/(1-exp(-0.693*14/half-life in days)) * $C_{312h}$. For the purpose of this analysis, the adalimumab (US) and adalimumab (EU) arms were combined.

For Study 20120262 (rheumatoid arthritis population) and Study 20120263 (plaque psoriasis population) observed trough data are from all subjects regardless of ant body status. Within each box, solid lines represent the median and dashed lines represent the mean. The mean and median data for the rheumatoid arthritis study are overlapping in the figure.

$C_{ss}$ = trough drug concentration at steady-state.

**Figure 30. Serum Trough Concentrations by Binding Anti-drug Antibody Status (Study 20120262 and Study 20120263 Pharmacokinetic Analysis Sets)**




Note: Negative and positive denotes anti-drug ant body status at the displayed time points. Within each box, solid lines represent the median and dashed lines represent the mean.

RA = rheumatoid arthritis.

### 5.2.3 PK Similarity Study Safety

In the PK study, there were no deaths and 1 serious adverse event of Grade 3 dermoid cyst was observed in the adalimumab (EU) arm, which was not considered related to the study drug. There were no treatment-emergent adverse events related to the study drug that led to discontinuation from the study (Table 9). Treatment-emergent adverse events were similarly reported for subjects in the ABP 501, adalimumab (US), and adalimumab (EU) groups (Table 10). There were no clinically relevant changes in clinical laboratory tests, electrocardiograms, vital signs, or physical examinations. No new safety risks were identified, and the safety profiles were generally similar across treatment groups. The adverse events seen in this study were consistent with the known safety profile of adalimumab as listed in the Humira United States Prescribing Information, 2016.

**Table 9. Overall Summary of Adverse Events (Study 20110217 Safety Population)**

| Adverse Event Category | ABP 501 (N = 67) n (%) | Adalimumab (US) (N = 69) n (%) | Adalimumab (EU) (N = 67) n (%) |
|---|---|---|---|
| Any adverse event | 39 (58.2) | 33 (47.8) | 46 (68.7) |
| Any Grade ≥ 3 adverse event | 0 (0.0) | 0 (0.0) | 1 (1.5) |
| Any treatment-related adverse event | 24 (35.8) | 17 (24.6) | 28 (41.8) |
| Any adverse event with outcome of death | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Any serious adverse event | 0 (0.0) | 0 (0.0) | 1 (1.5) |
| Any adverse event leading to discontinuation from study | 0 (0.0) | 0 (0.0) | 1 (1.5) |

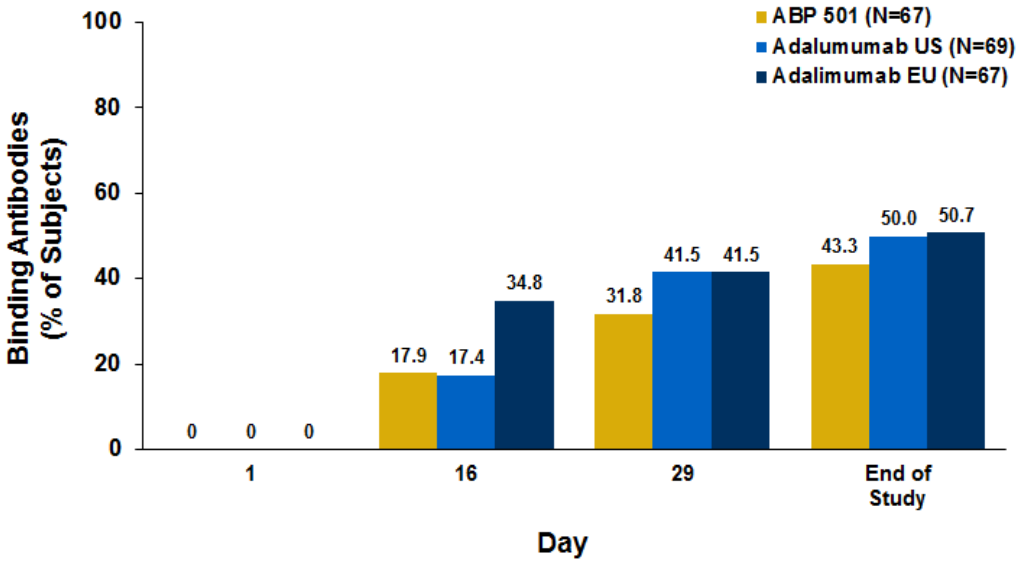
**Table 10. Treatment-emergent Adverse Events Reported in > 5% of Subjects in Any Treatment Group by Preferred Term (Safety Population) for Study 20110217**

| Preferred Term | ABP 501 (N = 67) n (%) | Adalimumab (US) (N = 69) n (%) | Adalimumab (EU) (N = 67) n (%) |
|---|---|---|---|
| Headache | 19 (28.4) | 16 (23.2) | 13 (19.4) |
| Oropharyngeal pain | 6 (9.0) | 6 (8.7) | 3 (4.5) |
| Sinus congestion | 6 (9.0) | 6 (8.7) | 0 |
| Nasopharyngitis | 4 (6.0) | 0 | 7 (10.4) |
| Nausea | 5 (7.5) | 2 (2.9) | 4 (6.0) |
| Diarrhea | 1 (1.5) | 1 (1.4) | 8 (11.9) |
| Vomiting | 1 (1.5) | 2 (2.9) | 5 (7.5) |
| Back pain | 1 (1.5) | 1 (1.4) | 5 (7.5) |
| Dizziness | 1 (1.5) | 1 (1.4) | 4 (6.0) |
| Dysmenorrhea | 1 (1.5) | 4 (5.8) | 1 (1.5) |
| Nasal congestion | 1 (1.5) | 4 (5.8) | 0 |

### 5.2.4 PK Similarity Immunogenicity

To detect anti-drug antibodies against administered ABP 501 and adalimumab, drug-specific immunoassays were employed (see Appendix 2 for a summary of the testing strategy and immunogenicity methods). In the PK similarity study, there were no pre-existing anti-drug antibodies detected in the baseline samples; all anti-drug antibodies developed after dosing with ABP 501 or adalimumab. The subjects who developed binding anti-drug antibodies over time are shown in Figure 31.

**Figure 31. Study 20110217 Anti-drug Antibody Summary (Safety Population)**

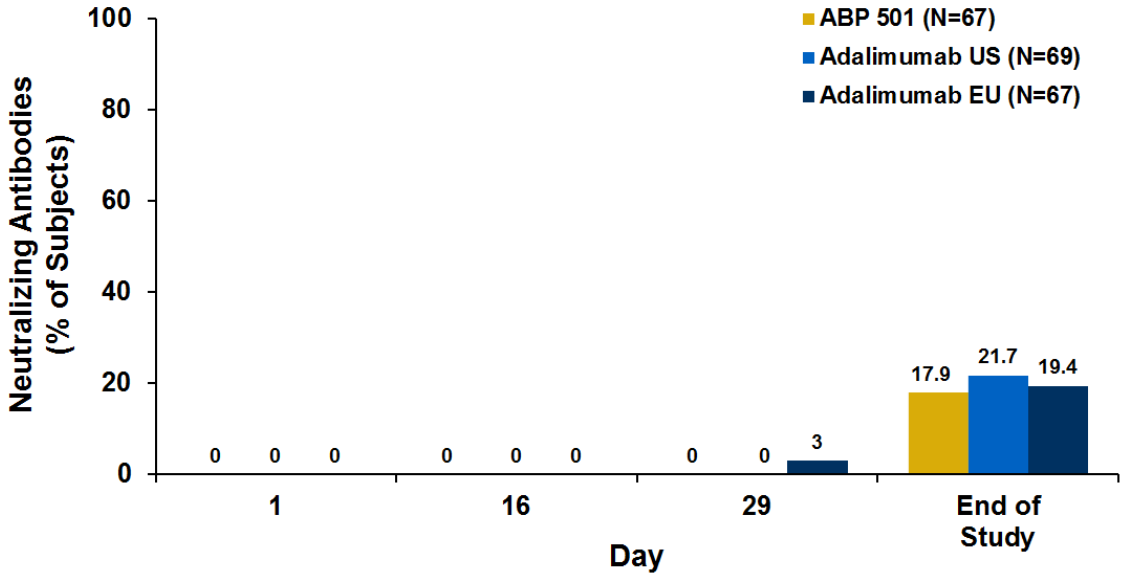



Note: End of study was day 63.

The incidence of binding anti-drug antibody development was similar for the subjects treated with ABP 501 or adalimumab. All antibody time points from all subjects, irrespective of treatment, were tested in the 3 immunoassays. Samples were scored positive for binding antibody if they were determined to be positive in any immunoassay. The overall rate of binding anti-drug antibody development at the end of study was 43.3%, 50.0%, and 50.7% after a single dose of ABP 501, adalimumab (US), or adalimumab (EU), respectively. In addition, cross-reactivity of product-specific antibodies was determined in all 3 immunoassays. Regardless of the treatment received (ABP 501 or adalimumab), the immunological cross-reactivity among anti-drug antibody-positive samples was highly similar, with > 90% of the anti-drug antibody results in agreement for all 3 immunoassays.

In addition, the cell-based assay for neutralizing activity detected a similar rate of neutralizing antibodies against all 3 products. The incidence of binding anti-drug antibody development and subjects positive for neutralizing anti-drug antibodies for ABP 501 and adalimumab were also similar at the end of study (Figure 32).

**Figure 32. Study 20110217 Neutralizing Antibody Summary (Safety Population)**




Note: End of study was day 63.

### 5.2.5 Conclusions

Based on the results from the PK study, the PK, safety, and immunogenicity of ABP 501 to adalimumab (US), and of ABP 501 to adalimumab (EU), were determined to be similar. Additionally, the PK, safety, and immunogenicity of adalimumab (US) and

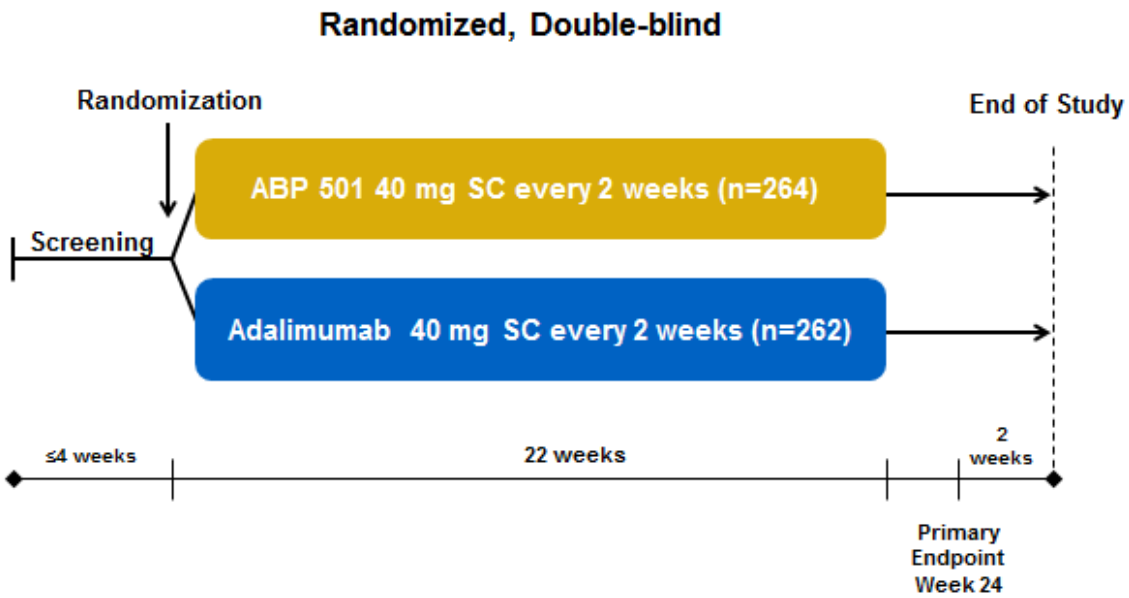
adalimumab (EU) were similar; thus, the comparative results for adalimumab sourced from different regions, combined with analytical data (see Section 3.2), justify the relevance of comparative clinical data between ABP 501 and adalimumab (EU) in the plaque psoriasis clinical study (Study 20120263).

## 5.3 Clinical Efficacy

### 5.3.1 Study 20120262 in Subjects with Moderately to Severely Active Rheumatoid Arthritis

Study 20120262 was a randomized, double-blind, active comparator-controlled study in subjects with moderately to severely active rheumatoid arthritis who had an inadequate response to methotrexate (Figure 33). The 26 week study was intended to demonstrate that there are no clinically meaningful differences between ABP 501 and adalimumab (US) in terms of efficacy, safety, and immunogenicity. The timing of the primary endpoint (ACR20 response at week 24) was consistent with the adalimumab clinical studies supporting global marketing approvals, which have shown that the maximal response occurs and stabilizes by week 24. Risk ratio analysis was chosen due to its efficiency in terms of statistical power.

**Figure 33. Design of Clinical Study 20120262 in Subjects with Moderately to Severely Active Rheumatoid Arthritis**




SC = subcutaneously.

#### 5.3.1.1 Key Design Features

**Inclusion/Exclusion Criteria**

Key inclusion criteria were:

- a diagnosis of rheumatoid arthritis by 2010 ACR/ European League Against Rheumatism (EULAR) classification criteria for at least 3 months
- active rheumatoid arthritis defined as 6 or more swollen joints and 6 or more tender joints at screening and baseline and at least 1 of the following:
  - erythrocyte sedimentation rate ≥ 28 mm/hour
  - serum C-reactive protein concentration > 1.0 mg/dL
- a positive rheumatoid factor or anti-cyclic citrullinated peptide result at screening
- methotrexate for at least 12 consecutive weeks (with a stable dose of 7.5 to 25 mg a week for at least 8 weeks) and willing to remain on a stable dose throughout the study
- no known history of active tuberculosis
- negative results for tuberculosis at screening

Key exclusion criteria were:

- class IV rheumatoid arthritis by ACR revised response criteria
- Felty's syndrome
- history of prosthetic or native joint infection
- use of prohibited medications within 28 days prior to the first dose of investigational product
- prior use of 2 or more biologic therapies for rheumatoid arthritis
- use of specified commercially available or investigational biologic therapies for rheumatoid arthritis within the protocol-specified time frame
- prior use of adalimumab or a biosimilar of adalimumab

**Study Size, Dosing, and Study Duration**

The study enrolled 526 subjects and randomized them in a 1:1 ratio to receive either ABP 501 or adalimumab 40 mg subcutaneously every 2 weeks in a double-blind fashion. The selected dose was the approved adalimumab dosing for treatment of moderately to severely active rheumatoid arthritis. Randomization was stratified by geographic region and prior biologic use for rheumatoid arthritis.

The sample size was chosen to achieve > 90% power to demonstrate equivalence at a 2-sided significance level of 0.05 for the primary efficacy endpoint (ACR20 at week 24 between ABP 501 and adalimumab) with an equivalence margin of (0.738, 1/0.738 [ie, 1.355]). An expected ACR20 response for both ABP 501 and adalimumab of 63% at week 24 and a 15% dropout by week 24 were assumed. The margin of 0.738 was

derived by taking into consideration the adalimumab effect size that could be reliably expected using historical studies and following the FDA guidance for non-inferiority studies to set this lower bound.

The study included 22 weeks of treatment followed by a safety follow-up period through week 26.

**Primary Efficacy Endpoint**

The primary efficacy endpoint of Study 20120262 was the risk ratio of ACR20 assessed at week 24, defined as the ratio of the proportion of subjects with an ACR20 response in the ABP 501 group divided by the proportion of subjects with an ACR20 response in the adalimumab group.

**Secondary Efficacy Endpoints**

Secondary efficacy endpoints included the risk ratio of ACR20 response at weeks 2 and 8, Disease Activity Score 28 C-reactive protein (DAS28-CRP) change from baseline at each time point (weeks 2, 4, 8, 12, 18, and 24), and risk ratio of ACR50 and ACR70 at week 24. Additional analyses for risk difference of ACR20 response were also performed. The analyses of the secondary efficacy endpoints were descriptive.

**Statistical Methodology**

Clinical equivalence was evaluated by the risk ratio analysis described above. Additionally, the risk difference of ACR20 with a margin of ± 12% was evaluated in response to the FDA's recommendation received after the database was locked.

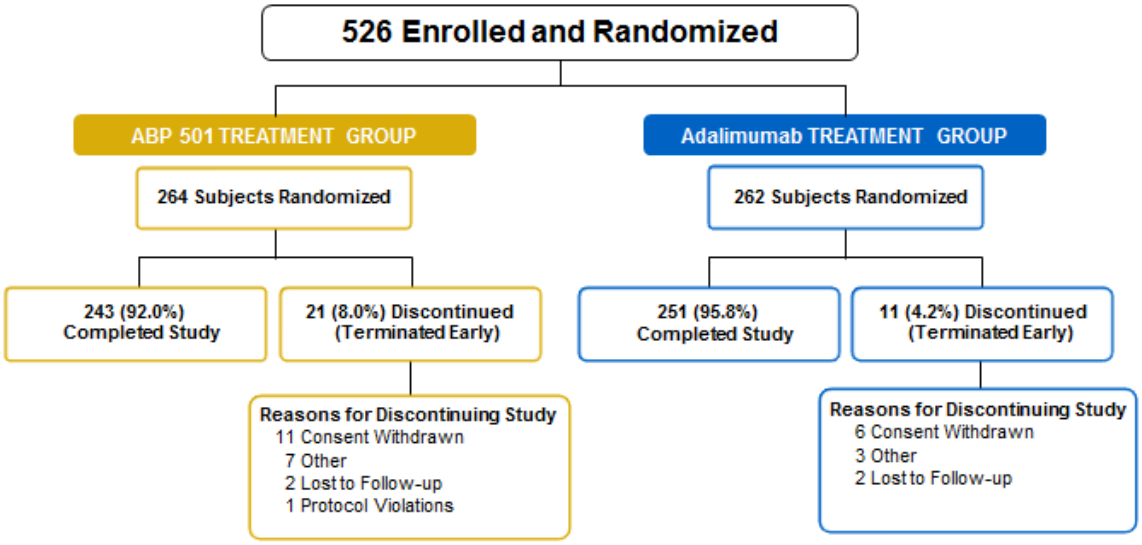
Sensitivity analyses of the key efficacy endpoints were also conducted using the full analysis set with non-responder imputation and the per protocol analysis set. The per protocol analysis set was based on the actual treatment received. Inferential analysis was performed only for the primary endpoint.

#### 5.3.1.2 Results

**Subject Disposition**

All randomized subjects in Study 20120262 were included in the full analysis set, and all received investigational product and were therefore included in the safety analysis. Completing the study were 494 subjects with only 32 subjects discontinuing the study early. Reasons for discontinuing the study included: consent withdrawn, protocol violations, lost to follow-up, and other. A study disposition summary diagram of the full analysis set is provided in Figure 34.

**Figure 34. Study 20120262 Summary of Study Disposition by Treatment (Full Analysis Set)**




**Demographic and Baseline Characteristics**

In general, subject demographics and baseline characteristics were comparable across treatment groups. A summary of key subject demographics and baseline characteristics is provided in Table 11.

Approximately 80% of the subjects were women. Most subjects were white, were not of Hispanic or Latino ethnicity, and were from Eastern Europe. All geographic regions were balanced across treatment arms. At baseline, the mean age was 55.9 years with a range of 21 to 80 years. More than 60% of subjects had rheumatoid arthritis for ≥ 5 years. The overall mean DAS28-CRP score at study entry was 5.67, indicative of active disease.

Over 90% of subjects were rheumatoid factor positive or anti-cyclic citrullinated peptide-positive at screening. The overall mean baseline methotrexate dose was 16.72 mg per week with a range of 7.5 to 25.0 mg per week. Overall, approximately 50% of the subjects were using oral corticosteroids, and approximately 60% – 64% were using non-steroidal anti-inflammatory drugs at baseline. Over 70% of subjects had not used prior biologics for rheumatoid arthritis.

**Table 11. Study 20120262 Summary of Demographic and Baseline Characteristics by Treatment (Full Analysis Set)**

| Variable | ABP 501 (N = 264) n (%) | Adalimumab (N = 262) n (%) |
|---|---|---|
| Sex, Women | 214 (81.1) | 212 (80.9) |
| Ethnicity, Not Hispanic or Latino | 230 (87.1) | 236 (90.1) |
| Race, White | 251 (95.1) | 249 (95.0) |
| Age, Mean (SD) years | 55.4 (11.88) | 56.3 (11.47) |
| Age Group, < 65 years | 205 (77.7) | 197 (75.2) |
| Body mass index, Mean (SD) | 27.80 (5.30) | 27.92 (5.57) |
| Region | | |
| Eastern Europe | 169 (64.0) | 168 (64.1) |
| Western Europe | 22 (8.3) | 20 (7.6) |
| North America | 72 (27.3) | 72 (27.5) |
| Prior biologic used for rheumatoid arthritis | 71 (26.9) | 74 (28.2) |
| Duration of rheumatoid arthritis, Mean (SD) years | 9.41 (8.08) | 9.37 (8.05) |
| ≥ 5 years | 163 (61.7) | 172 (65.6) |
| Used oral corticosteroids at baseline | 134 (50.8) | 130 (49.6) |
| Used NSAIDs at baseline | 159 (60.2) | 168 (64.1) |
| Baseline methotrexate dose mg/week, Mean (SD) | 16.9 (4.81) | 16.6 (4.93) |
| Rheumatoid factor status positive at screening | 243 (92.0) | 240 (91.6) |
| Anti-cyclic citrullinated peptide status positive at screening | 212 (80.3) | 230 (87.8) |
| DAS28-CRP, Mean (SD) | 5.66 (0.92) | 5.68 (0.91) |
| Swollen Joint Count, Mean (SD) | 14.7 (9.05) | 14.1 (7.98) |
| Tender Joint count, Mean (SD) | 24.3 (14.4) | 23.9 (13.5) |
| Subject Global Health Assessment, Mean (SD) | 6.5 (1.92) | 6.6 (1.86) |
| Investigator Global Health Assessment, Mean (SD) | 6.8 (1.29) | 6.7 (1.59) |
| Subject's assessment of disease-related pain, Mean (SD) | 58.3 (21.8) | 60.6 (22.4) |
| Health Assessment Questionnaire Disability Index, Mean (SD) | 1.48 (0.62) | 1.50 (0.65) |
| C-reactive protein mg/L, Mean (SD) | 13.9 (20.7) | 14.7 (19.4) |

DAS28-CRP = Disease Activity Score 28 C-reactive protein; NSAID = nonsteroidal anti-inflammatory drug; SD = standard deviation.

### Primary Efficacy Endpoint

A tabular summary of the results from the primary efficacy analysis is presented in Table 12.

**Table 12. Study 20120262 Analysis of ACR20 at Week 24 (Full Analysis Set, Last Observation Carried Forward)**

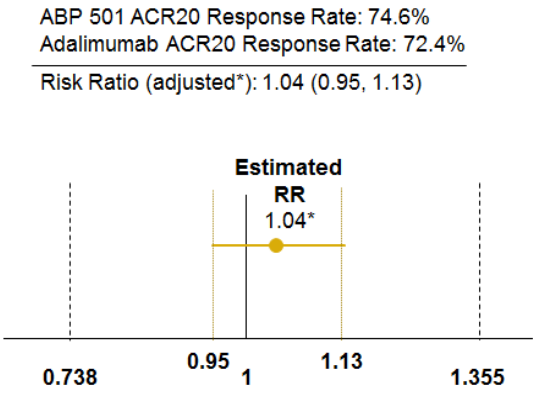
| Variable | ABP 501 (N = 264) | Adalimumab (N = 262) |
|---|---|---|
| ACR20 responder [n/N1 (%)] | 194/260 (74.6) | 189/261 (72.4) |
| Risk ratio of ACR20[a] | 1.039 | |
| 90% CI for risk ratio ACR20[a] | (0.954, 1.133) | |
| Risk difference of ACR20 (%)[a] | 2.604 | |
| 90% CI for risk difference ACR20 (%)[a] | (-3.728, 8.936) | |

ACR20 = 20% improvement in American College of Rheumatology core set measurements; CI = confidence interval; n = number of subjects meeting the criteria at the visit; N1 = number of subjects who were randomized and had an assessment at the visit.

[a] Based on a generalized linear model adjusted for geographic region and prior biologic use as covariates in the model.

As shown above, results from Study 20120262 confirmed the clinical equivalence of ABP 501 and adalimumab as measured by the risk ratio of ACR20 at week 24. At week 24, 74.6% of subjects in the ABP 501 group and 72.4% of subjects in the adalimumab group met the ACR20 response criteria. These proportions are consistent with the adalimumab responses reported in the literature. The 90% confidence interval (0.954, 1.133) was well within the pre-defined equivalence margin (0.738, 1.355), which demonstrates no clinically meaningful difference between ABP 501 and adalimumab (Figure 35).

**Figure 35. Study 20120262 Primary Endpoint: Risk Ratio of ACR20 at Week 24**




ACR20 = 20% improvement in American College of Rheumatology core set measurements; RR = risk ratio.

*ACR20 Risk ratio and its confidence interval were estimated with a statistical model adjusted for covariates.

To assess the robustness of the primary ACR20 results, the analysis was repeated using the full analysis set for observed cases, the full analysis set with non-responder imputation, and the per protocol analysis set for observed cases. In all 3 analyses, the 90% confidence interval of the risk ratio of ACR20 response at week 24 was within the pre-specified equivalence margin. Therefore, these analyses were consistent with the

primary analysis results that demonstrated clinical equivalence between ABP 501 and adalimumab.

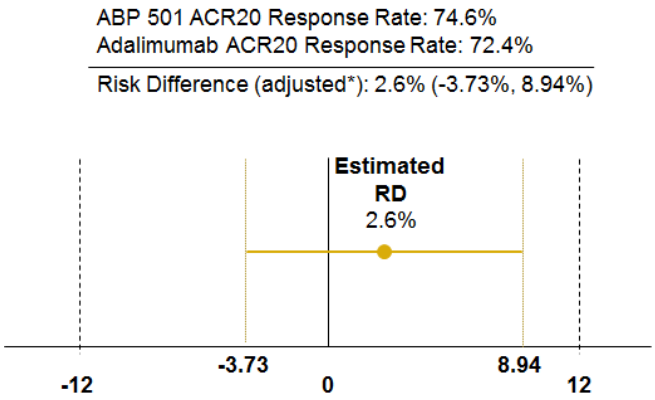
### Secondary Efficacy Endpoints

The results for all secondary efficacy endpoints were similar for the ABP 501 and adalimumab treatment groups.

#### ACR20

The percentage of subjects achieving ACR20 response across time is presented in Figure 37. At week 24, the risk difference of ACR20 for ABP 501 vs adalimumab (full analysis set, last observation carried forward) was 2.60% with the 2-sided 90% confidence interval of (-3.73%, 8.94%) (Table 12, Figure 36). The 90% confidence interval for risk difference of ACR20 at week 24 is within the FDA recommended margin of ± 12%, confirming the results of the primary analysis.

**Figure 36. Study 20120262 Risk Difference of ACR20 at Week 24**




ACR20 = 20% improvement in American College of Rheumatology core set measurements; RD = risk difference.
*ACR20 Risk Difference and its confidence interval were estimated with a statistical model adjusted for covariates.

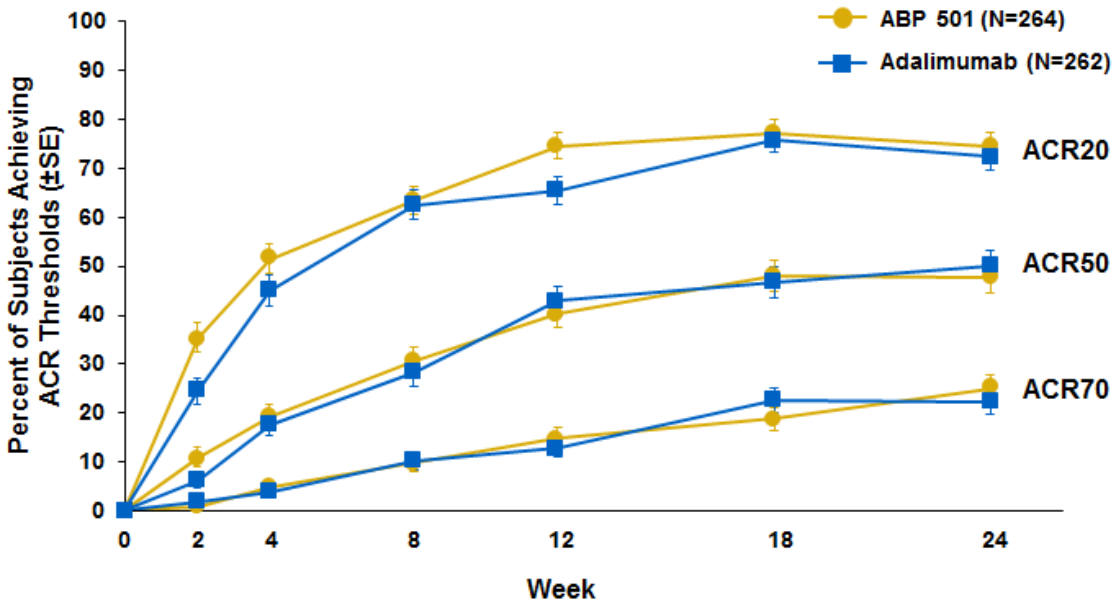
#### ACR50

The percentage of subjects achieving ACR50 response across time is presented graphically in Figure 37. At week 24, 49.2% of subjects in the ABP 501 group and 52.0% of subjects in the adalimumab group met the ACR50 response criteria.

#### ACR70

The percentage of subjects achieving ACR70 response across time is presented graphically in Figure 37. At week 24, 26.0% of subjects in the ABP 501 group and 22.9% of subjects in the adalimumab group met the ACR70 response criteria.

**Figure 37. Study 20120262 Percent of Subjects Achieving ACR20, ACR50, and ACR70 (Last Observation Carried Forward)**

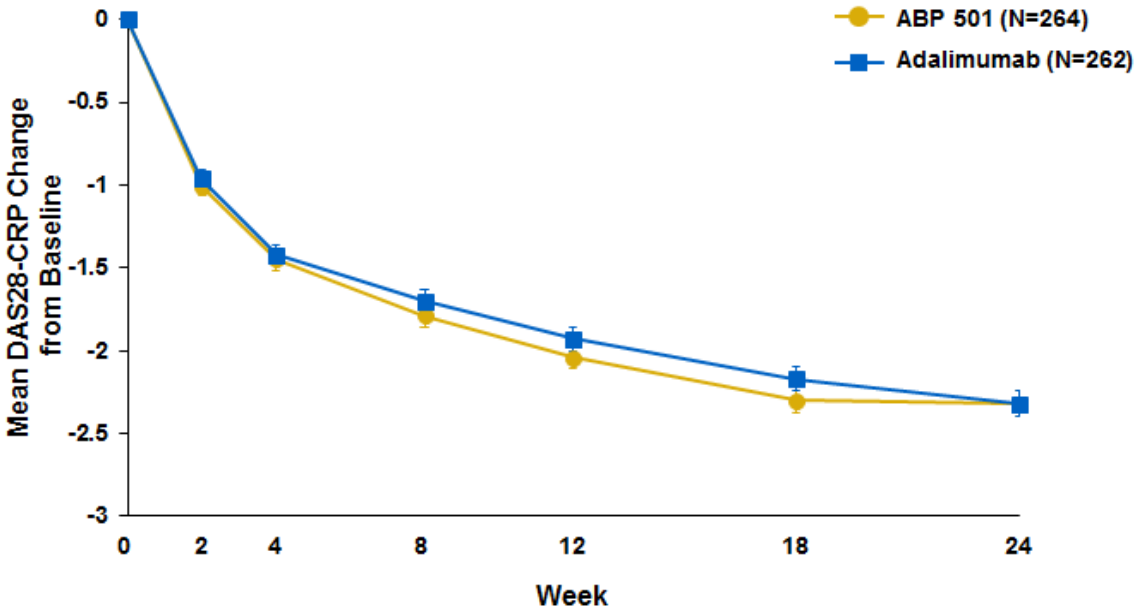



ACR = improvement in American College of Rheumatology; SE = standard error.

**Disease Activity Score 28 - C-reactive Protein Change from Baseline**

At baseline, the mean (standard deviation) DAS28-CRP score was similar between groups (5.66 [0.918] and 5.68 [0.911] for ABP 501 and adalimumab, respectively). The mean change from baseline of DAS28-CRP decreased over time in both treatment groups (full analysis set as observed) (Figure 38). At week 24, the mean change from baseline in DAS28-CRP was -2.32 in both groups, indicating the clinical equivalence between ABP 501 and adalimumab. Similar results were seen when DAS28-CRP change from baseline was analyzed using the per protocol analysis set, as well as when analyzed by prior biologic use, region, age, race, and sex.

**Figure 38. Study 20120262 Mean DAS28-CRP Change From Baseline (Full Analysis Set as Observed)**




DAS28-CRP = Disease Activity Score 28 – C-reactive protein.

#### 5.3.1.3 Conclusions

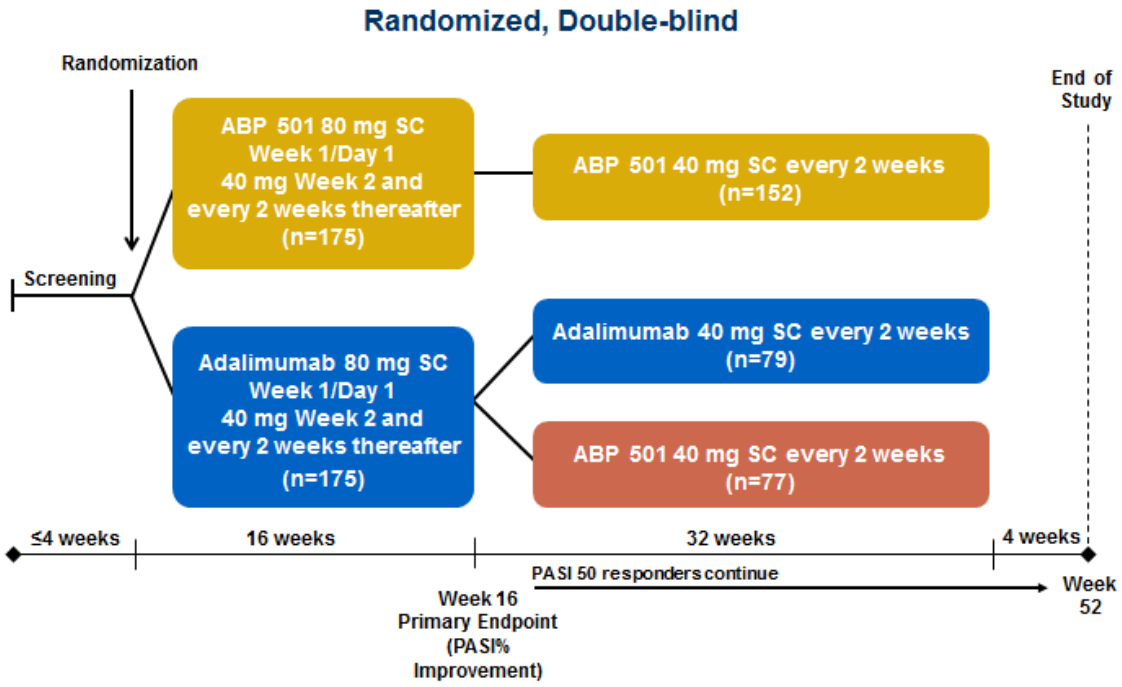
Clinical Study 20120262 in subjects with moderately to severely active rheumatoid arthritis demonstrated clinical equivalence between ABP 501 and adalimumab in the primary efficacy analysis of ACR20 at week 24. Similar results were observed for all sensitivity analyses, as well as for multiple covariates assessed and thus confirm the primary efficacy analysis. The results for the secondary efficacy endpoints, including ACR50, ACR70, and DAS28-CRP change from baseline were consistent with the primary efficacy analysis results and support the conclusion of clinical equivalence. The results from each treatment arm were also consistent with the results of the historical adalimumab clinical studies.

### 5.3.2 Study 20120263 in Subjects with Plaque Psoriasis

Study 20120263 was a randomized, double-blind, active comparator-controlled study in subjects with moderate to severe chronic plaque psoriasis. The 52-week study was designed to demonstrate that there are no clinically meaningful differences between ABP 501 and adalimumab (EU) in terms of safety, efficacy, and immunogenicity. The study also provides information on safety, efficacy, and immunogenicity in subjects originally randomized to adalimumab who underwent a single transition to ABP 501 at week 16 and continued receiving ABP 501 until week 52. A schematic of the study is shown in Figure 39. The primary endpoint of PASI percent improvement from baseline

at week 16 was chosen because, for the purposes of biosimilarity, it is considered sensitive, reliable, and appropriate for detecting clinically meaningful differences between ABP 501 and adalimumab in the moderate to severe chronic plaque psoriasis population. As a continuous measurement, the endpoint provides a full spectrum of response and allows the visualization of subtle differences in treatment effect. The endpoint is different from clinical trials for innovator programs that typically use binary PASI scores, such as PASI 75, PASI 90, or PASI 100, since the evidence generation is to show a clinical benefit against placebo or standard of care.

**Figure 39. Design of Study 20120263 in Subjects With Moderate to Severe Chronic Plaque Psoriasis**




PASI 50 = Psoriasis Area and Severity Index 50% improvement from baseline; SC = subcutaneously.

### 5.3.2.1 Key Design Features

**Inclusion/Exclusion Criteria**

Key inclusion criteria were:

- men or women aged 18 to 75 years of age with stable moderate to severe chronic plaque psoriasis for at least 6 months
- subjects who were candidates for systemic therapy or phototherapy
- subjects who had failed, had an inadequate response, were intolerant to, or contraindicated to at least 1 prior conventional anti-psoriatic systemic therapy
- subjects with at least 10% body surface area involvement
- subjects with a PASI score of at least 12

- subjects with a static Physician's Global Assessment score of at least 3 (moderate, severe, or very severe) at screening and baseline

Key exclusion criteria were:

- erythrodermic psoriasis
- pustular psoriasis
- guttate psoriasis
- medication-induced psoriasis
- prior use of 2 or more biologics for treatment of psoriasis, adalimumab, or a biosimilar of adalimumab

**Study Size, Dosing, and Duration**

Study 20120263 randomized 350 subjects in a 1:1 ratio to receive either ABP 501 or adalimumab 80 mg subcutaneously at week 1/day 1, and 40 mg subcutaneously at week 2 and every 2 weeks thereafter up to week 16 in a double-blind fashion. The dose was selected to be consistent with the recommended clinical dosing of adalimumab for the treatment of moderate to severe chronic plaque psoriasis. Randomization was stratified by geographic region and prior biologic use for plaque psoriasis.

At week 16, subjects with a PASI 50 or better response were eligible to remain on study for up to 52 weeks. Eligible subjects who continued treatment beyond week 16 were re-randomized so that all subjects initially randomized to ABP 501 continued treatment with ABP 501 (ABP 501/ABP 501 arm), and subjects initially randomized to adalimumab either continued treatment with adalimumab (adalimumab/adalimumab arm) or underwent a single transition to ABP 501 (adalimumab/ABP 501 arm). The study continued in a double-blind fashion for weeks 16 to through 52.

The sample size was chosen to achieve > 90% power to demonstrate equivalence at a significance level of 0.025 on the primary endpoint (PASI percent improvement from baseline at week 16) with margins of $\pm$ 15 (see statistical methodology section below).

**Primary Efficacy Endpoints**

The timing choice of the primary endpoint assessment of PASI percent improvement from baseline at week 16 was consistent with the historical adalimumab clinical trials, showing that time to full response in plaque psoriasis occurred and stabilized at week 16 and efficacy was significantly different from placebo and methotrexate.

**Secondary Efficacy Endpoints**

Secondary efficacy endpoints included PASI percent improvement from baseline at weeks 32 and 50 and PASI 75 response at weeks 16, 32, and 50. Additionally, static Physician's Global Assessment response (with 0 [clear] or 1 [almost clear] being a positive response) at weeks 16, 32, and 50 was a secondary efficacy endpoint along with percent of body surface area involvement at weeks 16, 32, and 50. Additional efficacy analyses of PASI 50, PASI 90, and PASI 100 responses at weeks 16, 32, and 50 were also performed. The analyses of the secondary efficacy endpoints were descriptive.

**Statistical Methodology**

Clinical equivalence of the primary efficacy endpoint was evaluated by comparing the 2-sided 95% confidence interval of the mean difference of PASI percent improvement from baseline at week 16 between ABP 501 and adalimumab with an equivalence margin of ± 15. The 2-sided 95% confidence interval of the group difference was estimated using an analysis of covariance model with baseline PASI score and stratification factors (geographic region and prior biologic use for plaque psoriasis) as covariates. The statistically derived margin followed the FDA guidance for non-inferiority studies and was also based on the adalimumab effect size that could be reliably expected using data from historical studies. The equivalence margin was then narrowed to ± 15 to provide for more robust clinical criteria to demonstrate no clinically meaningful differences between ABP 501 and adalimumab. This margin requires the point estimate of treatment difference and its 95% confidence interval to fall entirely within the margin, hence allows for a maximum difference of approximately ± 8 in the point estimate of the PASI percent improvement from baseline at week 16 between ABP 501 and adalimumab.

### 5.3.2.2 Results

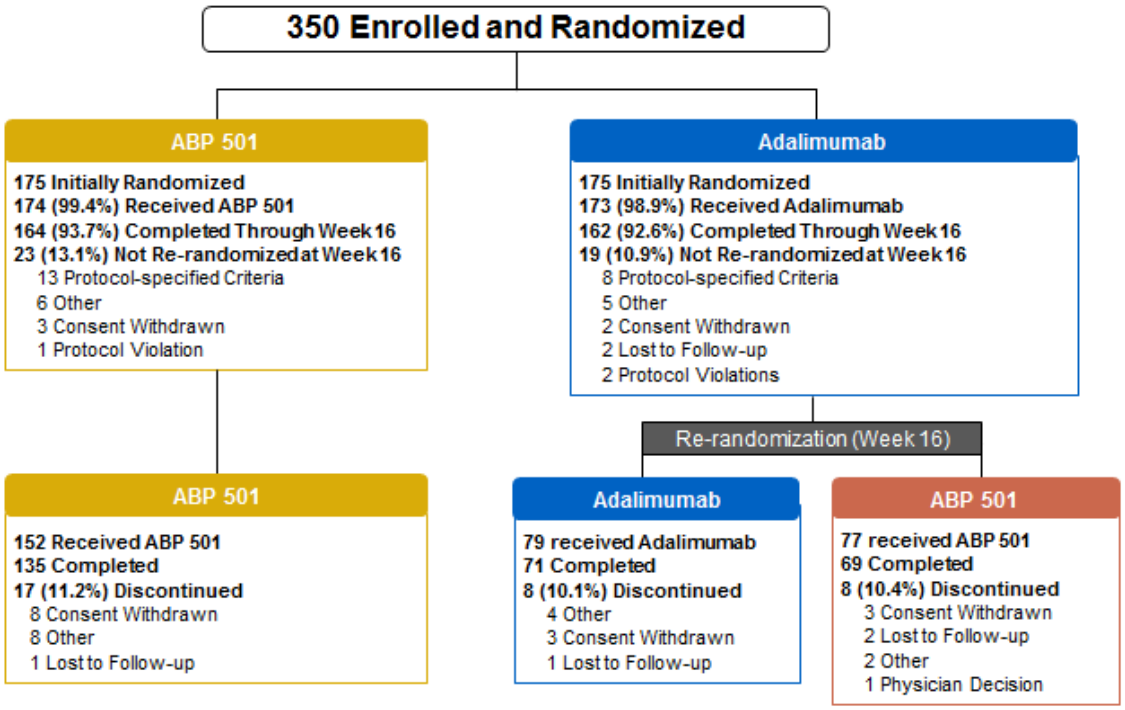
**Subject Disposition by Initial Treatment Across Entire study**

A total of 350 subjects (175 subjects in each treatment group) were initially randomized into Study 20120263 and 326 subjects completed the study through week 16. Most subjects were re-randomized at week 16. Some subjects were not re-randomized (23 subjects in the ABP 501 treatment group and 19 subjects in the adalimumab treatment group). The most common reason was the subjects did not meet the protocol specified criteria requirement of PASI 50 or better response (Figure 40).

### Subject Disposition by Initial/Re-randomized Treatment After Week 16

Of the 308 subjects re-randomized at week 16, 275 of 350 subjects completed the study. (Figure 40).

**Figure 40. Study 20120263 Summary of Study Disposition by Initial/Re-randomized Treatment (Full Analysis Set)**




### Demographic and Baseline Characteristics

Subject demographics and baseline characteristics were comparable across treatment groups by initial treatment and by initial/re-randomized treatment. A summary of key subject demographics and baseline characteristics by initial treatment is provided in Table 13.

**Table 13. Study 20120263 Summary of Demographic and Baseline Characteristics by Initial Treatment (Full Analysis Set)**

| Variable | ABP 501 (N = 175) n (%) | Adalimumab (N = 175) n (%) |
|---|---|---|
| Sex, Men | 112 (64.0) | 116 (66.3) |
| Ethnicity, Not Hispanic or Latino | 170 (97.1) | 169 (96.6) |
| Race, White | 167 (95.4) | 157 (89.7) |
| Age, Mean (SD) years | 45.1 (12.95) | 44.0 (13.68) |
| Age group, < 65 years | 164 (93.7) | 163 (93.1) |
| Region | | |
| Eastern Europe | 71 (40.6) | 70 (40.0) |
| Western Europe | 43 (24.6) | 43 (24.6) |
| Other | 61 (34.9) | 62 (35.4) |
| Duration of plaque psoriasis, Mean (SD) years | 19.85 (11.87) | 20.34 (13.48) |
| ≥ 5 years | 161 (92.0) | 160 (91.4) |
| Prior biological use for plaque psoriasis | 33 (18.9) | 30 (17.1) |
| PASI score, Mean (SD) | 19.68 (8.100) | 20.48 (7.880) |
| Body mass index, Mean (SD) | 29.7 (6.57) | 29.7 (5.83) |
| Body surface area affected by plaque psoriasis, Mean (SD) | 25.3 (15.02) | 28.5 (16.82) |
| Static Physician's Global Assessment | | |
| Moderate | 106 (60.6) | 102 (58.3) |
| Severe | 61 (34.9) | 61 (34.9) |
| Very severe | 7 (4.0) | 10 (5.7) |
| Prior use of systemic or photo therapies | 128 (73.1) | 135 (77.1) |
| Concomitant topical steroid used | 16 (9.1) | 20 (11.4) |

PASI = Psoriasis Area and Severity Index; SD = standard deviation.

Note: Treatment is based on initial randomized treatment. Percentages are based on number of initial randomized subjects.

**Demographic and Baseline Characteristics by Initial Treatment**

Of the 350 subjects randomized in Study 20120263, the majority of subjects were men. At baseline, mean age was 44.6 years. Most subjects were white, followed by Asian, and were not of Hispanic or Latino ethnicity.

At the time of study entry, the overall mean duration of plaque psoriasis was approximately 20 years, with a range of 0.7 to 59 years. The overall mean PASI score at study entry was 20.08, indicative of moderate to severe chronic plaque psoriasis. The overall mean percent of body surface area affected by plaque psoriasis was 26.9% with a range of 10% to 90%. The majority of subjects had static Physician's Global

Assessment score of moderate (59.4%) or severe (34.9%) and no subjects were scored as clear, almost clear, or mild.

Over 80% of subjects had not received prior biological treatment (63 [18.0%] in total had received), and slightly over 75% had prior use of systemic or phototherapies for plaque psoriasis. Concomitant topical steroids were used by approximately 10% of subjects in the study.

**Demographic and Baseline Characteristics by Initial/Re-randomized Treatment**

The demographics and baseline characteristics of the re-randomized groups were generally similar to those of the initial treatment groups.

**Primary Efficacy Endpoint**

A summary of the results from the primary efficacy endpoint is presented in Table 14 for the full analysis set (last observation carried forward). The efficacy analyses used the full analysis set, which included 350 subjects who were initially randomized through week 16 and the re-randomized analysis set which included 308 subjects (ie, 88.0% of the full analysis set) through the entire study.

**Table 14. Study 20120263 Summary of PASI Percent Improvement from Baseline Through Week 16 (Full Analysis Set, Last Observation Carried Forward)**

| | ABP 501 (N = 175) | | Adalimumab (N = 175) | |
|---|---|---|---|---|
| Time Point | PASI Score | PASI % Improvement from Baseline | PASI Score | PASI % Improvement from Baseline |
| Baseline, n | 174 | | 173 | |
| Mean (SD) | 19.68 (8.100) | | 20.48 (7.880) | |
| Week 16, n | 172 | 172 | 173 | 173 |
| Mean (SD) | 3.74 (5.094) | 80.91 (24.237) | 3.29 (5.795) | 83.06 (25.195) |
| Treatment difference[a] | | -2.18 | | |
| 95% CI for difference[a] | | (-7.39, 3.02) | | |

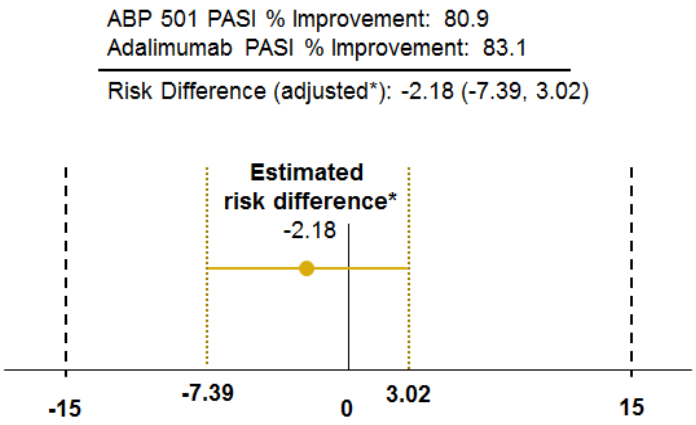
ANCOVA = analysis of covariance; CI = confidence interval; PASI = Psoriasis Area and Severity Index; SD = standard deviation.

[a] Estimated using ANCOVA model adjusted for the following factors: prior biologic use for psoriasis, region, and baseline PASI score.

As shown above, results from Study 20120263 in subjects with moderate to severe chronic plaque psoriasis confirmed clinical equivalence of ABP 501 to adalimumab. The mean PASI score at baseline was 19.68 and 20.48 for the ABP 501 and adalimumab treatment groups, respectively. At week 16, the mean PASI score for the ABP 501 treatment group was 3.74, an improvement of 80.91% compared with 3.29, an 83.06%

improvement for the adalimumab treatment group. The improvements are consistent with those reported for adalimumab in literature. The treatment difference between the 2 groups was -2.18 with a 2-sided 95% confidence interval of (-7.39, 3.02). The 95% confidence interval was well within the pre-defined equivalence margin of (-15, 15), thus establishing the clinical equivalence of ABP 501 and adalimumab (Table 14, Figure 41).

**Figure 41. Study 20120263 Primary Endpoint: PASI Percent Improvement at Week 16 (Full Analysis Set, Last Observation Carried Forward)**




PASI = Psoriasis Area and Severity Index.

*Risk difference and confidence interval were calculated with statistical model adjusted for covariates.

To assess the robustness of the primary PASI percent improvement from baseline results, a sensitivity analysis was performed using the full analysis set based on observed cases and the per protocol analysis set based on observed cases through week 16. When analyzed using the full analysis set as observed and the per protocol analysis set as observed, the treatment differences in PASI percent improvement from baseline between the ABP 501 and adalimumab treatment groups were -1.46 (2-sided 95% confidence interval: [-6.31, 3.39]) and -2.64 (2-sided 95% confidence interval [-6.89, 1.60]), respectively. For each of these populations, the 95% confidence intervals were within the pre-defined equivalence margins, and were consistent with the results of the primary analysis.

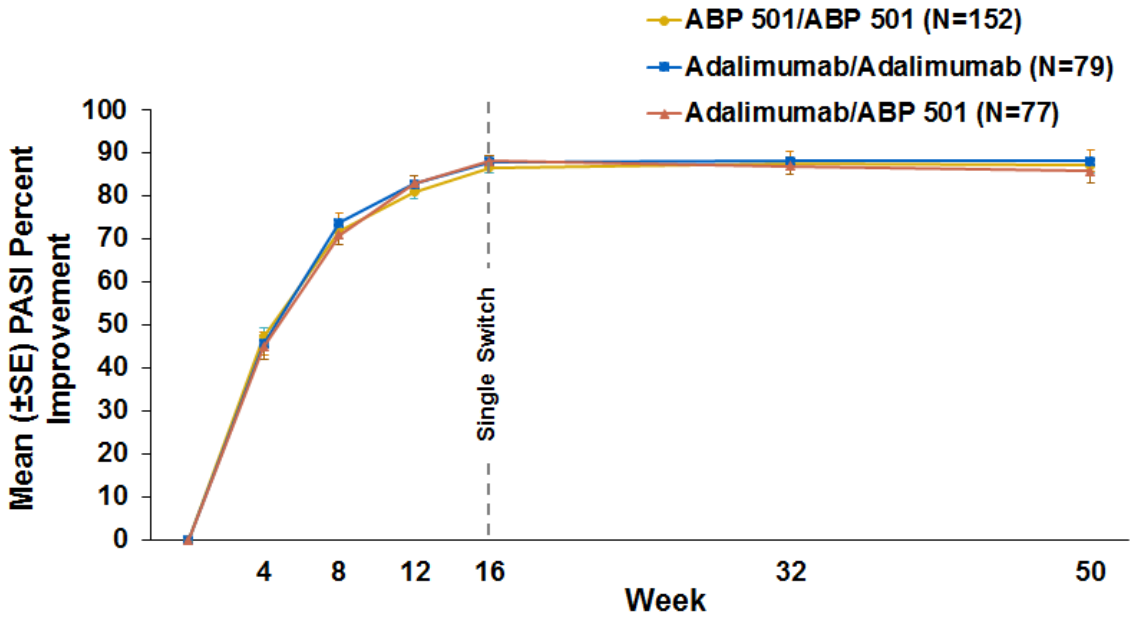
### Additional PASI Percent Improvement Analyses Used As Secondary Endpoints

PASI Percent Improvement From Baseline After Week 16 Through Entire Study

The PASI percent improvement from baseline values across the ABP 501/ABP 501, adalimumab/adalimumab, and adalimumab/ABP 501 treatment groups (re-randomized analysis set, as observed) were similar at week 32 (86.98% to 88.16%) and at week 50 (85.82% to 88.11%).

Mean PASI percent improvement from baseline over time through the entire study for the ABP 501/ABP 501, adalimumab/adalimumab, and adalimumab/ABP 501 treatment groups (re-randomized analysis set, as observed) is shown graphically in Figure 42.

**Figure 42. Study 20120263 Mean PASI Percent Improvement From Baseline Over Time – Through Entire Study (Re-randomized Analysis Set, as Observed)**




PASI = Psoriasis Area and Severity Index; SE = standard error.

### Additional PASI Assessments

PASI binary assessments at weeks 16, 32, and 50 were performed. Although these endpoints were not designed to have adequate power for reliable statistical comparisons, post-hoc analyses demonstrated that none of these binary assessments were statistically significantly different between the treatment groups.

PASI 50 Response

The PASI 50 response through week 16 (full analysis set, last observation carried forward) was 92.4% for the ABP 501 treatment group and 94.2% for the adalimumab treatment group.

The PASI 50 response across the ABP 501/ABP 501, adalimumab/adalimumab, and adalimumab/ABP 501 treatment groups (re-randomized analysis set, as observed), were similar at week 32 (94.4% to 95.8%) and at week 50 (92.8% to 96.3%).

A summary of the PASI 50 binary assessments at week 16 is shown in Figure 43 and at week 50 in Figure 44.

PASI 75 Response

The PASI 75 response at week 16 (full analysis set, last observation carried forward) was achieved for 74.4% (128 of 172) of subjects in the ABP 501 treatment group and 82.7% (143 of 173) of subjects for the adalimumab treatment group.

The PASI 75 responses across the ABP 501/ABP 501, adalimumab/adalimumab, and adalimumab/ABP 501 treatment groups (re-randomized analysis set, as observed), were similar at week 16 (81.6% to 89.6%), week 32 (82.5% to 84.7%), and at week 50 (81.2% to 87.1%).

A summary of the PASI 75 binary assessments at week 16 is shown in Figure 43 and at week 50 in Figure 44.

PASI 90 Response

In a post hoc analysis the PASI 90 response through week 16 (full analysis set, last observation carried forward) was 47.1% for the ABP 501 group and 47.4% for the adalimumab treatment group.

Based on the re-randomized analysis set (as observed), the PASI 90 responses across the ABP 501/ABP 501, adalimumab/adalimumab, and adalimumab/ABP 501 treatment groups were similar at week 32 (57.7% to 65.3%) and at week 50 (59.0% to 66.7%).

A summary of the PASI 90 binary assessments at week 16 is shown in Figure 43 and at week 50 in Figure 44.

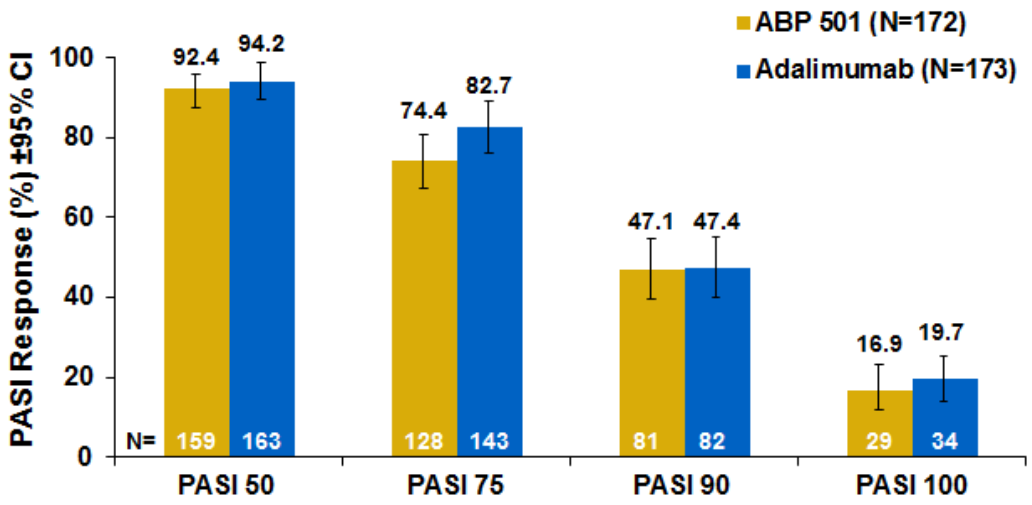
PASI 100 Response

In a post hoc analysis the PASI 100 response through week 16 (full analysis set, last observation carried forward) was 16.9% for the ABP 501 group and 19.7% for the adalimumab treatment group.

Based on the re-randomized analysis set (as observed), the PASI 100 responses across the ABP 501/ABP 501, adalimumab/adalimumab, and adalimumab/ABP 501 treatment groups were similar at week 32 (25.4% to 33.3%) and at week 50 (32.8% to 35.7%).

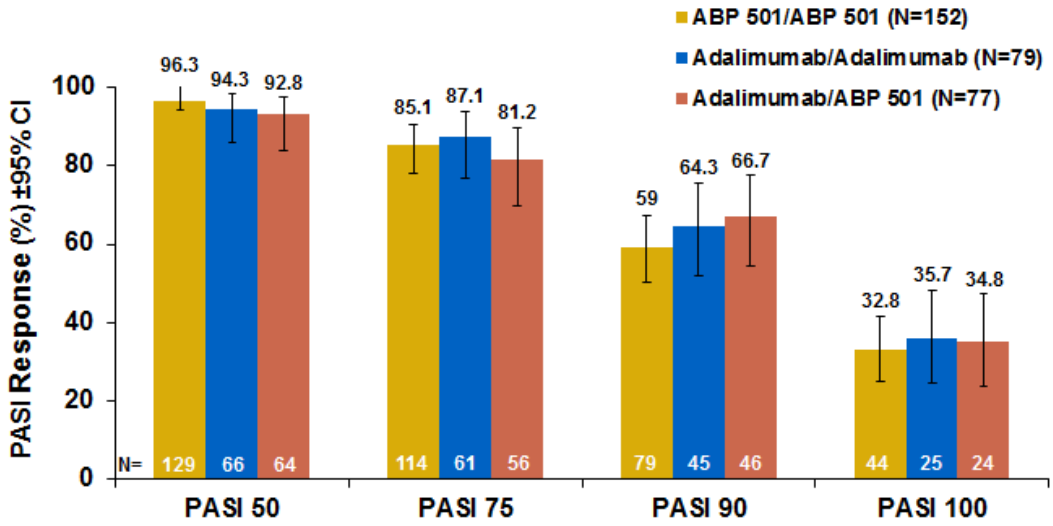
A summary of the PASI 100 binary assessments at week 16 is shown in Figure 43 and at week 50 in Figure 44.

**Figure 43. Study 20120263 Summary of Additional PASI Assessments at Week 16**




CI = confidence interval; PASI = Psoriasis Area and Severity Index.

**Figure 44. Study 20120263 Summary of Additional PASI Assessments at Week 50**




CI = confidence interval; PASI = Psoriasis Area and Severity Index.

### Additional Secondary Efficacy Endpoints

Additional secondary efficacy endpoints included static Physician's Global Assessment responses at weeks 16, 32, and 50; and body surface area involvement at weeks 16, 32, and 50. The results for all secondary efficacy endpoints were similar for the ABP 501 and adalimumab treatment groups. Analyses of efficacy endpoints through weeks 32 and 50 confirmed long-term efficacy after a single transition from adalimumab to ABP 501. These data were descriptive only and no inferential analyses were performed.

Static Physician's Global Assessment

At baseline, approximately 60% of subjects had a static Physician's Global Assessment of moderate (ABP 501, 60.9%, 106 of 174 subjects; adalimumab, 59.0%, 102 of 173 subjects). No subjects in either group were assessed as clear, almost clear, or mild. At week 16, the majority of subjects (full analysis set, last observation carried forward) had a positive static Physician's Global Assessment response (defined as clear or almost clear) (ABP 501, 58.7%, 101 of 172 subjects; adalimumab, 65.4%, 113 of 173 subjects).

The static Physician's Global Assessment positive responses across the ABP 501/ABP 501, adalimumab/adalimumab, and adalimumab/ABP 501 treatment groups (re-randomized analysis set, as observed) were similar at week 32 (66.4% to 72.2%) and at week 50 (68.7% to 74.3%).

Percent Body Surface Area Involvement

Based on the full analysis set at baseline, the mean (standard deviation) percent body surface area affected by plaque psoriasis was similar for the ABP 501 and adalimumab treatment groups (25.3% [15.02%] and 28.5% [16.82%], respectively). At week 16, the mean (standard deviation) percent body surface area affected by plaque psoriasis was 7.4% (11.22%) for the ABP 501 treatment group and 6.4% (10.97%) for the adalimumab treatment group.

The mean percent body surface area values affected by plaque psoriasis across the ABP 501/ABP 501, adalimumab/adalimumab, and adalimumab/ABP 501 treatment groups (re-randomized analysis set, as observed), were similar at week 32 (5.12% to 8.59%) and at week 50 (5.86% to 7.25%).

#### 5.3.2.3 Conclusions

Clinical Study 20120263 in subjects with moderate to severe chronic plaque psoriasis demonstrated clinical equivalence between ABP 501 and adalimumab in the primary efficacy analysis of PASI percent improvement from baseline at week 16. Similar results were observed for all sensitivity analyses, as well as for multiple covariates assessed. Similar long-term efficacy after a single transition from adalimumab to ABP 501 at week 16 was confirmed based on analyses of efficacy endpoints through week 32 and week 50. The results for all secondary efficacy endpoints further confirmed similarity for ABP 501 and adalimumab. The results from each treatment arm were also consistent with the results of the historical adalimumab clinical studies.

## 5.4 Safety and Immunogenicity

### 5.4.1 Safety

The safety data for ABP 501 were collected in the 3 clinical trials: PK similarity Study 20110217 in healthy subjects, Study 20120262 in subjects with moderately to severely active rheumatoid arthritis who have had an inadequate response to methotrexate, and Study 20120263 in subjects with moderate to severe chronic plaque psoriasis. Please refer to Section 5.3.1.1 and Section 5.3.2.1 for inclusion/exclusion criteria for rheumatoid arthritis and psoriasis studies, respectively.

The safety analysis was performed on the safety population, defined as all patients who received at least 1 dose of any of the investigational products. The safety endpoints included treatment-emergent adverse events (adverse events that began or increased in severity or frequency at or after the time of first treatment but on or within 28 days following the last dose of study treatment), serious adverse events, clinically significant changes in laboratory values, and changes in vital signs.

#### 5.4.1.1 Subject Exposure

The safety population includes 1076 subjects who received at least 1 dose of investigational product. Treatment with ABP 501 included 582 subjects in all 3 studies with a total exposure of 281.53 patient years.

In the single-dose PK similarity Study 20110217, 67 subjects received ABP 501. Across the 2 studies in therapeutic indications, 264 subjects were exposed to ABP 501 in rheumatoid arthritis Study 20120262, and 251 subjects in plaque psoriasis Study 20120263. In Study 20120263, 77 of the subjects also transitioned from treatment with adalimumab to ABP 501 (adalimumab/ABP 501) at week 16.

#### 5.4.1.2 Overview of Safety

The safety profile for ABP 501 is consistent with the known safety profile of adalimumab and no new safety signals were identified (Humira United States Prescribing Information). Please refer to Section 5.2.3 for an overview of safety in the PK similarity study in healthy subjects. In the rheumatoid arthritis and plaque psoriasis studies, the incidence of treatment-emergent adverse events, grade $\geq$ 3 events, serious adverse events, adverse events leading to discontinuation, and adverse events of interest were similar between ABP 501 and adalimumab (Table 15). There were no deaths in the clinical program.

## Table 15. Overview of Adverse Events in the Rheumatoid Arthritis and Plaque Psoriasis Studies

| | Rheumatoid Arthritis Study 20120262 | | Plaque Psoriasis Study 20120263 | | | | |
|---|---|---|---|---|---|---|---|
| | | | Through Week 16 | | Weeks 16 - 52 (Re-randomized) | | |
| Adverse Event Category | ABP 501 N = 264 | Adalimumab N= 262 | ABP 501 N = 174 | Adalimumab N = 173 | ABP 501/ ABP 501 N = 152 | Adalimumab/ Adalimumab N = 79 | Adalimumab/ ABP 501 N = 77 |
| Number of subjects with TEAE, n (%) | 132 (50.0) | 143 (54.6) | 117 (67.2) | 110 (63.6) | 108 (71.1) | 52 (65.8) | 54 (70.1) |
| Number of subjects with grade ≥ 3 TEAE, n (%) | 9 (3.4) | 17 (6.5) | 8 (4.6) | 5 (2.9) | 7 (4.6) | 2 (2.5) | 3 (3.9) |
| Number of subjects with SAE, n (%) | 10 (3.8) | 13 (5.0) | 6 (3.4) | 5 (2.9) | 4 (2.6) | 4 (5.1) | 4 (5.2) |
| Number of subjects with TEAE leading to study discontinuation, n (%) | 7 (2.7) | 2 (0.8) | 7 (4.0) | 5 (2.9) | 4 (2.6) | 1 (1.3) | 2 (2.6) |
| Number of subjects with adverse event of interest, n (%) | 80 (30.3) | 94 (35.9) | 68 (39.1) | 69 (39.9) | 75 (49.3) | 31 (39.2) | 39 (50.6) |

SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Note: Adverse events are coded using MedDRA version 17.1. Only treatment-emergent adverse events from the safety analysis set are summarized. For each adverse event category, subjects are included only once even if they experienced multiple events in that category. Adverse events of interest were pre-specified based on the known safety risks for adalimumab.

**Treatment-emergent Adverse Events**

The incidence of treatment-emergent adverse events in the rheumatoid arthritis and plaque psoriasis studies was similar between ABP 501 and adalimumab. The adverse events reported by system organ class (≥ 5% in any treatment group) are shown in Table 16. The most frequently reported adverse events in the rheumatoid arthritis study were nasopharyngitis, headache, and arthralgia, and the rates were similar between the treatment groups. The most frequently reported adverse events in the plaque psoriasis study through week 16 were nasopharyngitis, headache, upper respiratory tract infection and arthralgia; and week 16-52 were nasopharyngitis, upper respiratory tract infection, psoriasis, headache, diarrhea, arthralgia, and back pain. No trends in adverse events were seen, and the safety profile was consistent between ABP 501 and adalimumab, including in the subset of subjects who underwent the single transition in treatment from adalimumab to ABP 501.

## Table 16. Treatment-emergent Adverse Events, by System Organ Class (≥ 5%) in the Rheumatoid Arthritis and Plaque Psoriasis Studies

| | Rheumatoid Arthritis Study 20120262 | | Plaque Psoriasis Study 20120263 | | | | |
|---|---|---|---|---|---|---|---|
| | | | Through Week 16 | | Weeks 16 - 52 (Re-randomized) | | |
| System Organ Class | ABP 501 N = 264 | Adalimumab N= 262 | ABP 501 N = 174 | Adalimumab N = 173 | ABP 501/ ABP 501 N = 152 | Adalimumab/ Adalimumab N = 79 | Adalimumab/ ABP 501 N = 77 |
| Any adverse event | 132 (50.0) | 143 (54.6) | 117 (67.2) | 110 (63.6) | 108 (71.1) | 52 (65.8) | 54 (70.1) |
| Infections and infestations | 61 (23.1) | 68 (26.0) | 59 (33.9) | 58 (33.5) | 67 (44.1) | 29 (36.7) | 37 (48.1) |
| Musculoskeletal and connective tissue disorders | 27 (10.2) | 36 (13.7) | 23 (13.2) | 19 (11.0) | 21 (13.8) | 18 (22.8) | 11 (14.3) |
| Gastrointestinal disorders | 21 (8.0) | 24 (9.2) | 17 (9.8) | 27 (15.6) | 17 (11.2) | 9 (11.4) | 12 (15.6) |
| Skin and subcutaneous tissue disorders | 23 (8.7) | 19 (7.3) | 14 (8.0) | 20 (11.6) | 24 (15.8) | 9 (11.4) | 13 (16.9) |
| General disorders and administration site conditions | 15 (5.7) | 26 (9.9) | 12 (6.9) | 16 (9.2) | 8 (5.3) | 5 (6.3) | 3 (3.9) |
| Respiratory, thoracic, and mediastinal disorders | 18 (6.8) | 18 (6.9) | 7 (4.0) | 12 (6.9) | 10 (6.6) | 3 (3.8) | 6 (7.8) |
| Investigations | 19 (7.2) | 14 (5.3) | 10 (5.7) | 8 (4.6) | 10 (6.6) | 3 (3.8) | 3 (3.9) |
| Nervous system disorders | 18 (6.8) | 15 (5.7) | 17 (9.8) | 23 (13.3) | 11 (7.2) | 10 (12.7) | 3 (3.9) |
| Injury, poisoning, and procedural complications | 14 (5.3) | 10 (3.8) | 9 (5.2) | 12 (6.9) | 13 (8.6) | 3 (3.8) | 6 (7.8) |

Note: Adverse events are coded using MedDRA version 17.1. Only treatment-emergent adverse events from the safety analysis set are summarized. For each system organ class, subjects are included only once even if they experienced multiple events in that class.

**Severe Adverse Events (Grade ≥ 3)**

The incidence of severe adverse events was similar between ABP 501 and adalimumab in both the rheumatoid arthritis and plaque psoriasis studies, as shown in Table 15.

In the rheumatoid arthritis Study 20120262, the proportion of subjects who experienced grade ≥ 3 events was similar between the treatment groups (3.4% ABP 501 and 6.5% adalimumab). The most common grade ≥ 3 adverse events by preferred term (≥ 2 subjects in either treatment group) were hypertension and sepsis (each of these events occurred in 2 subjects in the ABP 501 group).

In the plaque psoriasis Study 20120263, the proportion of subjects who experienced grade ≥ 3 events was similar between the treatment groups through week 16 and weeks 16 - 52. There were no grade 3 events reported in more than 1 subject in any treatment group.

**Serious Adverse Events**

The serious adverse events in the rheumatoid arthritis and plaque psoriasis studies were infrequent and similar in the ABP 501 and adalimumab treatment groups. Table 17 shows the incidence of serious adverse events reported in either study, by system organ class.

## Table 17. Serious Adverse Events by System Organ Class and Treatment in the Rheumatoid Arthritis and Plaque Psoriasis Studies

| | Rheumatoid Arthritis Study 20120262 | | Plaque Psoriasis Study 20120263 | | | | |
|---|---|---|---|---|---|---|---|
| | | | Through Week 16 | | Weeks 16 - 52 (Re-randomized) | | |
| System Organ Class | ABP 501 N = 264 n (%) | Adalimumab N= 262 n (%) | ABP 501 N = 174 n (%) | Adalimumab N = 173 n (%) | ABP 501/ ABP 501 N = 152 n (%) | Adalimumab/ Adalimumab N = 79 n (%) | Adalimumab/ ABP 501 N = 77 n (%) |
| Any serious adverse event | 10 (3.8) | 13 (5.0) | 6 (3.4) | 5 (2.9) | 4 (2.6) | 4 (5.1) | 4 (5.2) |
| Cardiac disorders | 1 (0.4) | 4 (1.5) | 2 (1.1) | 0 (0.0) | 1 (0.7) | 0 (0.0) | 0 (0.0) |
| Infections and infestations | 2 (0.8) | 3 (1.1) | 2 (1.1) | 1 (0.6) | 1 (0.7) | 0 (0.0) | 2 (2.6) |
| Injury, poisoning, and procedural complications | 2 (0.8) | 1 (0.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Musculoskeletal and connective tissue disorders | 0 (0.0) | 3 (1.1) | 0 (0.0) | 2 (1.2) | 1 (0.7) | 1 (1.3) | 0 (0.0) |
| Gastrointestinal disorders | 1 (0.4) | 1 (0.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Immune system disorders | 1 (0.4) | 1 (0.4) | 1 (0.6) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Vascular disorders | 2 (0.8) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Blood and lymphatic disorders | 1 (0.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Nervous system disorders | 1 (0.4) | 0 (0.0) | 0 (0.0) | 1 (0.6) | 1 (0.7) | 2 (2.5) | 1 (1.3) |
| Neoplasms benign, malignant and unspecified (including cysts and polyps) | 0 (0.0) | 0 (0.0) | 1 (0.6) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Reproductive system and breast disorders | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.6) | 0 (0.0) | 0 (0.0) | 1 (1.3) |
| Respiratory, thoracic and mediastinal disorders | 0 (0.0) | 0 (0.0) | 1 (0.6) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Hepatobiliary disorders | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.7) | 0 (0.0) | 0 (0.0) |
| Metabolism and nutrition disorders | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.7) | 0 (0.0) | 0 (0.0) |
| Psychiatric disorders | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (1.3) | 0 (0.0) |

Note: Adverse events are coded using MedDRA version 17.1. Only treatment-emergent adverse events from the safety analysis set are summarized. For each system organ class term, subjects are included only once, even if they experienced multiple events in that system organ class.

### Adverse Events Leading to Study Discontinuation

Adverse events leading to discontinuation from the rheumatoid arthritis and plaque psoriasis studies were infrequent in both the ABP 501 and adalimumab treatment groups in each study (Table 15). Events were generally single events experienced by single subjects; and there was no trend in adverse events leading to discontinuation.

### Adverse Events of Interest

Adverse events of interest are those that are known safety risks for adalimumab based on the Warnings and Precautions section of the Humira United States Prescribing Information, 2016. These events are displayed in Table 18; the overall rates were generally balanced between ABP 501 and adalimumab, and there were no clinically meaningful differences between ABP 501 and adalimumab in either study.

## Table 18. Adverse Events of Interest in the Rheumatoid Arthritis and Plaque Psoriasis Studies

| | Rheumatoid Arthritis Study 20120262 | | Plaque Psoriasis Study 20120263 | | | | |
|---|---|---|---|---|---|---|---|
| | | | Through Week 16 | | Weeks 16 - 52 (Re-randomized) | | |
| Event of Interest Category | ABP 501 N = 264 n (%) | Adalimumab N= 262 n (%) | ABP 501 N = 174 n (%) | Adalimumab N = 173 n (%) | ABP 501/ ABP 501 N = 152 n (%) | Adalimumab/ Adalimumab N = 79 n (%) | Adalimumab/ ABP 501 N = 77 n (%) |
| Any adverse event of interest | 80 (30.3) | 94 (35.9) | 68 (39.1) | 69 (39.9) | 75 (49.3) | 31 (39.2) | 39 (50.6) |
| Infections and infestations | 61 (23.1) | 68 (26.0) | 59 (33.9) | 58 (33.5) | 67 (44.1) | 29 (36.7) | 37 (48.1) |
| Hypersensitivity | 14 (5.3) | 10 (3.8) | 8 (4.6) | 7 (4.0) | 8 (5.3) | 2 (2.5) | 3 (3.9) |
| Liver enzyme elevations | 13 (4.9) | 10 (3.8) | 4 (2.3) | 2 (1.2) | 9 (5.9) | 2 (2.5) | 2 (2.6) |
| Injection site reactions | 6 (2.3) | 13 (5.0) | 3 (1.7) | 9 (5.2) | 2 (1.3) | 3 (3.8) | 0 (0.0) |
| Hematological reactions | 5 (1.9) | 5 (1.9) | 0 (0.0) | 3 (1.7) | 0 (0.0) | 1 (1.3) | 1 (1.3) |
| Malignancies | 1 (0.4) | 1 (0.4) | 1 (0.6) | 1 (0.6) | 1 (0.7) | 0 (0.0) | 0 (0.0) |
| Heart failure | 1 (0.4) | 2 (0.8) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Demyelinating diseases | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Lupus-like syndromes | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |

Note: Adverse events are coded using MedDRA version 17.1. Only treatment-emergent adverse events from the safety analysis set are summarized. For each event of interest category, subjects are included only once even if they experienced multiple events in that category. Events of interest are aggregated using Standardised MedDRA Queries (SMQs) that are groupings of MedDRA terms, ordinarily at the preferred term level, that relate to a defined medical condition or area of interest (SMQ Introductory Guide, Version 16.0, March 2013, MSSO-DI-6226-16.0.0).

**Infections**

The rate and severity of infections were similar between treatment groups in the rheumatoid arthritis and plaque psoriasis studies.

In the rheumatoid arthritis study, most of the infections were viral, with the most commonly reported adverse event of nasopharyngitis. Serious infections were balanced (ABP 501, 0.8%; adalimumab, 1.1%). There was 1 opportunistic infection in each group (ABP 501, grade 2 lymphadenopathy due to cytomegalovirus; adalimumab, grade 3 pneumocystis carinii pneumonia).

In the plaque psoriasis study, most infections were viral with the most commonly reported adverse events being nasopharyngitis and upper respiratory tract infection. Serious infections were infrequent through week 16, occurring in 2 subjects in the ABP 501 group (appendicitis and postoperative abscess) and 1 subject in the adalimumab group (bronchitis). Additionally, 1 subject in the adalimumab group experienced a grade 3 event of latent tuberculosis that led to study discontinuation. After week 16, serious infections were also infrequent, occurring in 1 subject in the ABP 501/ABP 501 group (diverticulitis), no reports in the adalimumab/adalimumab group, and 2 subjects in the adalimumab/ABP 501 group (ophthalmic herpes zoster and urinary tract infection). There were only 2 cases of opportunistic infection (both mentioned above): ophthalmic herpes zoster in a subject receiving ABP 501 and latent tuberculosis in a subject receiving adalimumab.

**Hypersensitivity**

The rate and severity of hypersensitivity reactions were similar between ABP 501 and adalimumab in the rheumatoid arthritis and plaque psoriasis studies. Almost all events were grade 1 or grade 2 in severity, and resolved while the subjects continued treatment in each group.

In the rheumatoid arthritis study, the most commonly reported event of hypersensitivity was rash. There was one grade 1 event of hypersensitivity reported as serious in ABP 501 group and described as “generalized allergic reaction."

In the plaque psoriasis study through week 16, the most commonly reported adverse events of hypersensitivity were eczema, allergic conjunctivitis, contact dermatitis, and rash. There was 1 event of grade 4 anaphylaxis in the ABP 501 group (based on Sampson’s criteria) and 1 event of grade 3 rash in the adalimumab group. After week 16, the most commonly reported adverse events of hypersensitivity were contact

dermatitis, rash, and urticaria. There was 1 subject with grade 3 contact dermatitis in the ABP 501/ABP 501 group.

**Liver Enzyme Elevation**

The rate and severity of liver enzyme elevations were similar between ABP 501 and adalimumab in the rheumatoid arthritis and plaque psoriasis studies. Almost all events were grade 1 or grade 2 in severity, were mostly transient, and most resolved while the subjects continued treatment.

In the rheumatoid arthritis study, there were no serious events of liver enzyme elevation in either group. In the psoriasis study through week 16, 1 subject in the ABP 501 group experienced a grade 3 increase in hepatic enzymes (AST and GGT) and 1 subject in the adalimumab group experienced grade 3 increase in transaminases. After week 16, 1 subject in the ABP 501/ABP 501 group experienced a grade 3 serious adverse event of drug-induced liver injury due to increases in AST and ALT; but the case did not satisfy Hy's Law as there were no associated increases in bilirubin. The subject began the study with normal liver function tests, then on day 108, the subject developed elevated AST and ALT. The event of drug-induced liver injury led to discontinuation of investigational product, however, liver enzyme levels continued to increase. Concomitant medications of metoprolol and ramipril were discontinued, and within 3 days ALT and AST levels began to decrease and resolved on day 197. The subject was discontinued early from the study.

**Malignancies**

Malignancy adverse events were infrequent and balanced across treatment arms in the rheumatoid arthritis and plaque psoriasis studies. Most were benign skin tumors. No cases of lymphoma were observed in the ABP 501 clinical program.

In the rheumatoid arthritis study, 1 subject in the ABP 501 group had 2 events: basal cell carcinoma and squamous cell carcinoma of the skin, and 1 subject in the adalimumab group had squamous cell carcinoma of the skin. In the psoriasis study through week 16, 1 event of malignant melanoma (lentigo maligna) was reported in the ABP 501 group as serious, and 1 event of Bowen's disease (benign skin tumor) was reported in the adalimumab group. After week 16 in the psoriasis study, 1 subject in the ABP 501/ABP 501 group had squamous cell carcinoma of the skin (sebaceous adenoma).

**Laboratory Values and Vital Signs**

In the rheumatoid arthritis studies, no clinically meaningful changes were observed in the ABP 501 or adalimumab groups in laboratory values (hematology and chemistry) or vital signs (pulse, systolic and diastolic blood pressure, respiration rate, and temperature) from baseline to the end of the studies.

#### 5.4.1.3 Safety Conclusions

The type, severity, and incidence of treatment-emergent adverse events, serious adverse events, adverse events of interest, as well as clinically significant changes in laboratory values, and changes in vital signs with ABP 501 and adalimumab were similar within the rheumatoid arthritis and plaque psoriasis studies. Additionally, in the plaque psoriasis study, the safety profile of subjects who underwent a single transition from adalimumab to ABP 501 was similar to those who continued on their original treatment. No new safety risks were identified and the safety of ABP 501 is consistent with the known safety profile of adalimumab. Hence, it is concluded that there are no clinically meaningful differences in safety between ABP 501 and adalimumab.

### 5.4.2 Immunogenicity

Assessment of immunogenicity was a secondary objective of the rheumatoid arthritis and plaque psoriasis clinical studies.

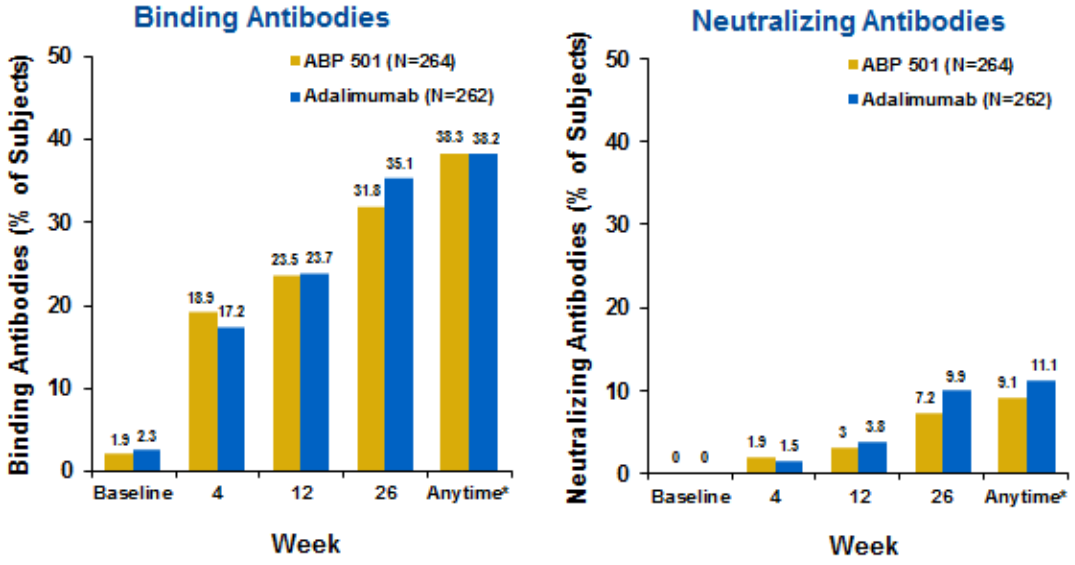
The assays used for anti-drug antibody detection in the rheumatoid arthritis and plaque psoriasis clinical studies (Study 20120262 and Study 20120263) were sensitive, drug-tolerant, and robust to detect differences in immunogenicity between ABP 501 and the comparator drug. In addition, a validated assay for detecting neutralizing anti-drug antibodies was used for testing the binding antibody positive samples (see Appendix 2 for a summary of the testing strategy and immunogenicity methods). Regardless of treatment received (ABP 501 or adalimumab), the immunological cross-reactivity among anti-drug antibody-positive samples was highly similar, with > 90% of the anti-drug antibody-positive results in agreement with the immunoassays tested across all 3 ABP 501 clinical studies. All samples were tested in both ABP 501 and adalimumab assays. The reported immunogenicity rates reflect results tested positive with either assay.

#### 5.4.2.1 Study 20120262 in Rheumatoid Arthritis

In the rheumatoid arthritis population (Study 20120262), the immunogenicity assessment results were descriptive in nature. The immunogenicity comparison of ABP 501 and adalimumab in rheumatoid arthritis showed the anti-drug antibody rate in a population on

background methotrexate. An overall summary of the anti-drug antibody and neutralizing antibody rates for ABP 501 and adalimumab is presented in Figure 45. The observed incidence rates for anti-drug antibodies were higher than originally described for adalimumab, as was observed in the PK similarity and plaque psoriasis studies, because of the highly sensitive and drug tolerant assays currently used. The incidence of binding and neutralizing antibodies was similar between ABP 501 and adalimumab-treated subjects.

**Figure 45. Study 20120262 Binding and Neutralizing Anti-Drug Antibodies**




* Post-baseline.

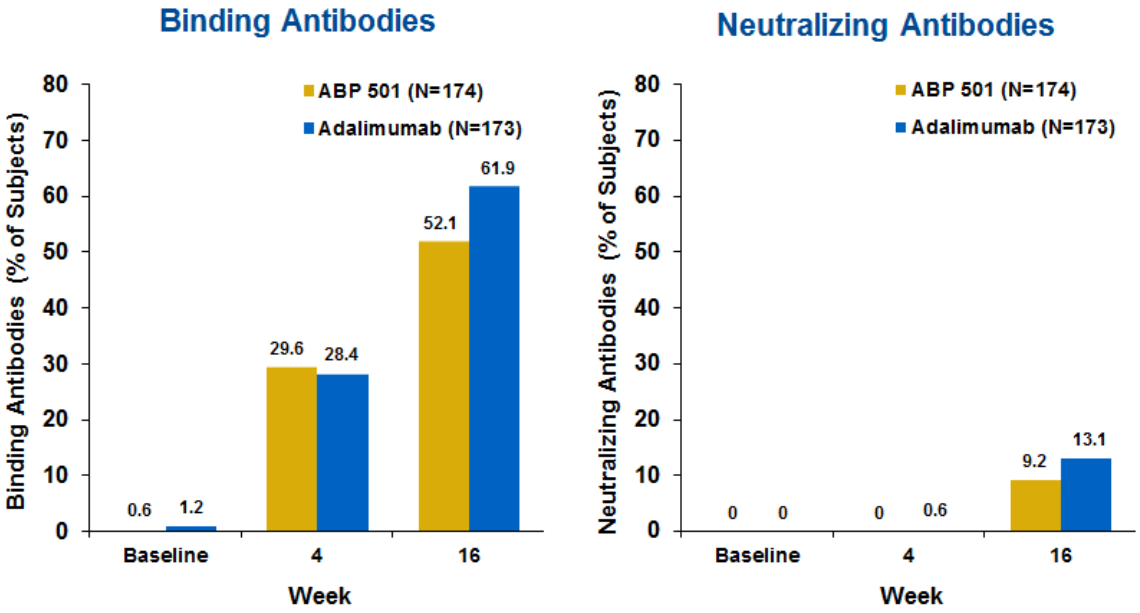
### 5.4.2.2 Study 20120263 in Plaque Psoriasis

In the plaque psoriasis population (Study 20120263), the immunogenicity assessment was descriptive in nature. The immunogenicity comparison of ABP 501 and adalimumab in plaque psoriasis showed the anti-drug antibody rate in a population without other systemic immunosuppression.

The incidence of binding or neutralizing antibodies in subjects treated with drug was comparable between ABP 501 and adalimumab through the primary analysis at week 16 and across treatment groups post week 16. As shown in Figure 46, there was an increased incidence of binding and neutralizing antibodies with continued exposure from week 4 through week 16. This increasing rate of binding and neutralizing antibody development with exposure is known for adalimumab. The observed incidence rates for anti-drug antibodies were higher than originally described for adalimumab, as was observed in the PK similarity and rheumatoid arthrtitis studies, because of the highly

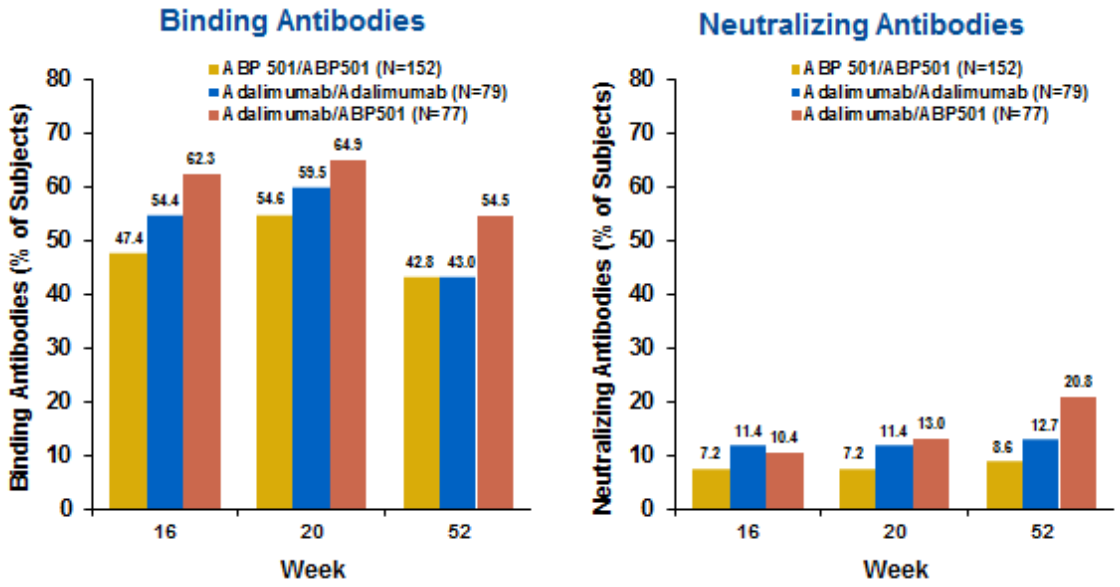
sensitive and drug tolerant assays currently used. However, the importance of the immunogencitiy assessment for biosimilarity is the rates of anti-drug antibodies between the biosimilar and the reference product, and they are similar between ABP 501 and adalimumab.

**Figure 46. Study 20120263 Binding and Neutralizing Anti-drug Antibodies Summary Results Anti-Drug Antibodies Through Week 16**



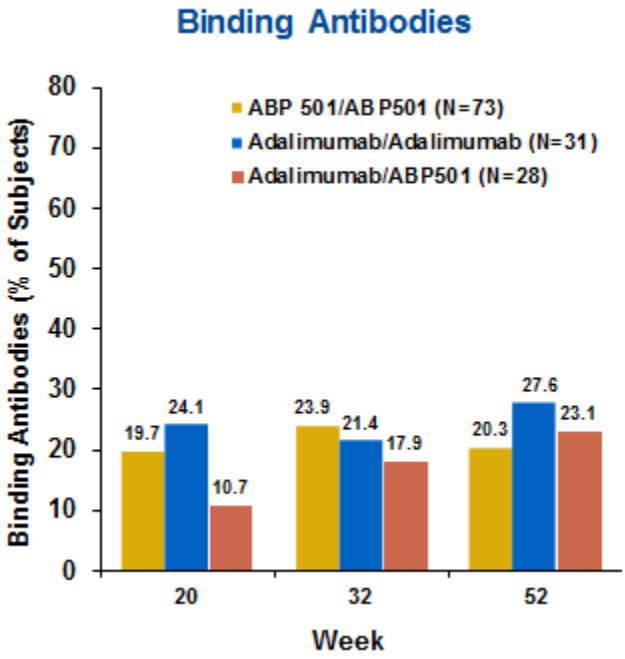

At week 16, subjects in the adalimumab arm were re-randomized to either transition to ABP 501 or continue on adalimumab treatment. This re-randomization led to more subjects with binding anti-drug antibodies in the adalimumab/ABP 501 arm even prior to receiving the first dose after the transition. As shown in Figure 47, the rate of binding antibodies that formed after the transition at week 16 was comparable from week 20 through week 52, with the rates similar to those at week 16 at the time of the re-randomization. Subjects with binding antibodies are predisposed to form neutralizing antibodies and, since the subjects in the transition arm had higher binding anti-drug antibodies at week 16 due to re-randomization, this resulted in higher neutralizing anti-drug antibodies by the end of the study.

**Figure 47. Study 20120263 Binding and Neutralizing Anti-drug Antibodies Summary Results From Week 16 Through Week 52**



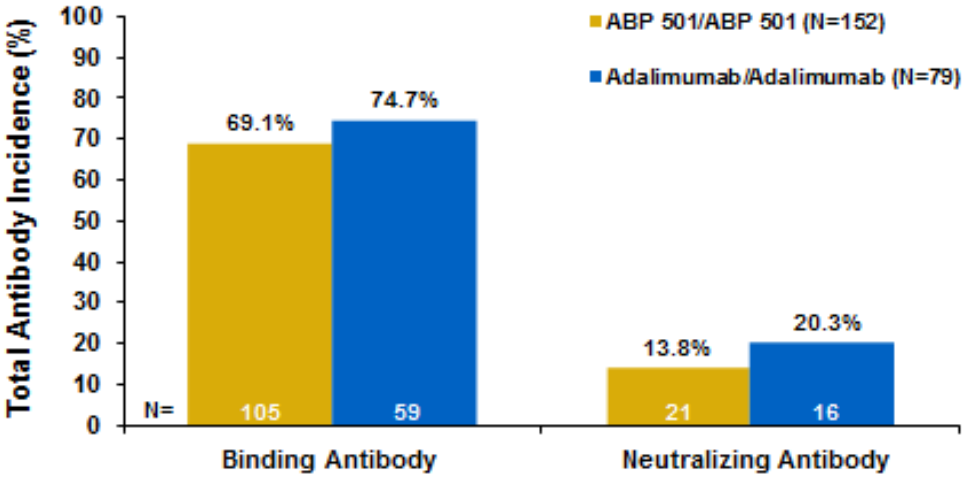

To further evaluate any potential effect of transitioning from adalimumab to ABP 501, a post-hoc analysis of the rate of anti-drug antibody development was performed on the subjects who were anti-drug antibody-negative through week 16. This provided an assessment of any effect without bias introduced by existing anti-drug antibodies. After transitioning from adalimumab to ABP 501, the incidence of new anti-drug antibodies in these subjects was similar to non-transitioned subjects (Figure 48). None of the subjects who were anti-drug antibody-negative through week 16 developed neutralizing antibodies by the time of the last assessment at week 52.

**Figure 48. Study 20120263 Binding Anti-drug Antibodies Summary Results Week 20 to Week 52 for Subjects Anti-drug Antibody-negative Through Week 16**




Finally, the data presented in Figure 49 shows the rate of binding and neutralizing anti-drug antibodies for subjects who maintained treatment with ABP 501 or adalimumab through week 52. The percentage of subjects positive anytime in the study for binding and neutralizing antibodies was comparable through week 52, regardless of treatment received.

**Figure 49. Study 20120263 Binding and Neutralizing Anti-drug Antibodies Summary Results Anytime from Week 0 to Week 52**



#### 5.4.2.3 Immunogenicity Conclusions

Amgen concludes that the formation of anti-drug antibodies, both binding and neutralizing, was comparable for ABP 501 and adalimumab in the 3 clinical trials, which included the PK similarity (Study 20110217), rheumatoid arthritis (Study 20120262), and plaque psoriasis (Study 20120263) studies. In addition, the development of binding and neutralizing anti-drug antibodies was similar when subjects were transitioned from adalimumab to ABP 501.

## 6. EXTRAPOLATION

The purpose of this section is to summarize the scientific justification for extrapolating claims of safety and efficacy to conditions of use approved for adalimumab that were not studied in the ABP 501 clinical program. In agreement with FDA guidance, this section considers the current knowledge of ABP 501 and adalimumab, regarding mechanisms of action, PK, toxicities (safety profiles), immunogenicity, efficacy, and other factors that may affect safety or effectiveness in each indication. As described in the preceding sections, a high degree of similarity in structure, purity, and functional attributes, PK, immunogenicity, safety, and efficacy has been demonstrated for ABP 501 (in sensitive assays and representative patient populations). This similarity, together with the current knowledge of adalimumab provides confidence that ABP 501 will have equivalent safety and efficacy as adalimumab in all approved indications of the reference product.

### 6.1 Analytical and Functional Similarity

The ABP 501 analytical similarity assessment demonstrated a high degree of similarity with minimal analytical differences between ABP 501 and adalimumab (Section 3.2.1). Furthermore, the functional similarity comparison of ABP 501 to adalimumab, which included assessments of multiple TNFα-dependent functions, including those that are relevant to all indications of use for adalimumab, also demonstrated high similarity between the products.

The functional similarity of ABP 501 compared to adalimumab was demonstrated with respect to binding and neutralizing TNFα (Section 3.2.2). The binding kinetics to soluble TNFα were also demonstrated to be similar. In addition, further characterization assays were performed in order to confirm similarity in neutralizing TNFα activity in both NFκB-dependent and NFκB-independent signaling pathways (Table 3). Thus, ABP 501 is highly similar to adalimumab in binding to and neutralizing soluble TNFα, inclusive of both reported downstream signaling pathways. This provides a key component of scientific justification supporting extrapolation to all based on an understanding of the primary mechanism of action.

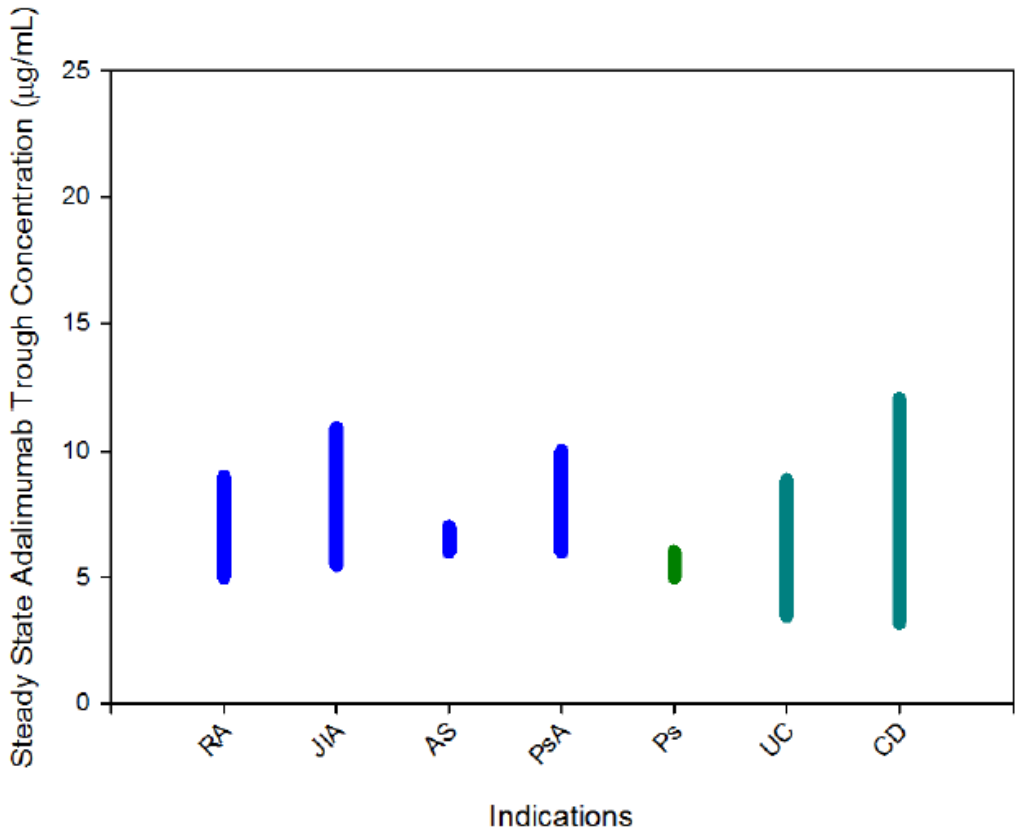
For the inflammatory bowel disease indications, binding of adalimumab to transmembrane TNFα may contribute to clinical efficacy via cell depletion (ADCC and CDC), decreased proliferation of transmembrane TNFα-expressing cells, or a combination of the different mechanisms (Table 3). ABP 501 and adalimumab have demonstrated high similarity in functional assays testing not only binding to

transmembrane TNFα but also the induction of the effector functions, ADCC and CDC, and decreased proliferation in a mixed lymphocyte reaction (Section 3.2.2). Similarity in these functions, along with similarity in binding and neutralizing soluble TNFα, provides justification supporting extrapolation to the inflammatory bowel disease indications (ulcerative colitis and Crohn's disease).

## 6.2 Clinical Pharmacology

As discussed in Section 5.2, literature on the adalimumab PK profile in healthy subjects and across therapeutic indications has been evaluated for factors that could influence exposure. Of the factors investigated, the presence of anti-drug antibodies, concomitant use of methotrexate, body weight, and serum albumin levels have been determined to affect adalimumab PK. The disease type is not a statistically significant factor affecting PK variability and the mean trough concentrations across populations are consistent (Figure 50).

**Figure 50. Steady-state Trough Adalimumab Concentration Ranges in Different Patient Populations**




AS = ankylosing spondylitis; CD = Crohn's disease; JIA = juvenile idiopathic arthritis; PsA = psoriatic arthritis; Ps = plaque psoriasis; RA = rheumatoid arthritis; UC = ulcerative colitis.

Note: The presented data represent the ranges of data located in: Humira Summary of Product Characteristics, 2016; Humira United States Prescribing Information, 2016; Baert et al, 2014; Karmiris et al, 2009. The dosing regimens were the same as found in the approved Humira United States Prescr bing Information, 2016.

The PK similarity of ABP 501 to adalimumab was established in healthy subjects, as discussed in Section 5.2.1. Additionally, trough PK sampling was incorporated into the clinical studies in the rheumatoid arthritis and plaque psoriasis populations. The trough PK levels observed in these studies also demonstrated similarity between ABP 501 and adalimumab. These comparative PK data in sensitive and representative populations, combined with the knowledge of the PK profiles of adalimumab in different patient populations indicate that ABP 501 will retain a PK profile similar to adalimumab in all indications for which ABP 501 licensure is sought.

### 6.3 Safety

There are known adalimumab safety risks that are common across indications and dosing regimens, as discussed in Section 5.4.1 of this document.

Study 20120262 in subjects with moderately to severely active rheumatoid arthritis receiving concomitant methotrexate is considered sensitive and relevant for assessing potential differences in safety profiles of ABP 501 and adalimumab. Study 20120263, in subjects with moderate to severe chronic plaque psoriasis, assessed safety in younger subjects with fewer comorbidities and without concomitant immunosuppressive therapy, and is also considered relevant and informative for assessing differences in safety profiles of ABP 501 and adalimumab. In addition, subjects in Study 20120263 were administered a loading dose of 80 mg of study drug, similar to the dosing regimen for Crohn's disease and ulcerative colitis, thus providing additional justification for expected similarity in indications requiring higher doses to be administered.

No clinically meaningful differences in toxicities were observed between treatment groups in the rheumatoid arthritis and plaque psoriasis studies, and the adverse events from both studies were in agreement with the known safety profile of adalimumab. Given the consistency of the safety profiles in adalimumab's approved indications, and the similarity in the safety profiles in the 2 ABP 501 clinical studies, the ABP 501 safety profile is expected to be the same for all indications for which ABP 501 licensure is sought.

### 6.4 Immunogenicity

Adalimumab is known to be an immunogenic product that patients can readily develop binding or neutralizing anti-drug antibodies. The incidence rate of developing these anti-drug antibodies is reduced in subjects receiving concomitant immunosuppression, and this effect is seen across arthritides, dermatologic conditions, and inflammatory bowel diseases. The incidence rate of anti-drug antibodies against adalimumab is

generally similar across conditions of use when compared using the same immunoassay and considering the use of immunosuppressants, though small differences are reported for different populations (Humira United States Prescribing Information, 2016).

The 2 ABP 501 clinical studies provided a population (rheumatoid arthritis) with concomitant immunosuppressant therapy (methotrexate) and a population without concomitant immunosuppressant therapy (plaque psoriasis). Both clinical studies demonstrated the expected high rates of anti-drug antibody formation based on the knowledge of adalimumab, providing a robust ability to detect potential differences, if they existed, between ABP 501 and adalimumab. The results of the comparison in both clinical studies, demonstrated similar rates of both binding and neutralizing anti-drug antibody formation, covering 2 different treatment paradigms (with and without immunosuppression) and different populations of patients (see Section 5.4.2). Therefore the immunogenicity of ABP 501 is expected to be similar to adalimumab in all populations and indications of use for which licensure is sought.

### 6.5 Clinical Efficacy

The response rates to adalimumab are comparable across all arthritides indications, and the dosing regimens across the adult indications in arthritides are identical.
Study 20120262 in subjects with moderately to severely active rheumatoid arthritis demonstrated clinical equivalence in efficacy between ABP 501 and adalimumab. These efficacy results are considered predictive of similar efficacy in all other arthritic conditions of use for which ABP 501 licensure is sought.

Study 20120263 in subjects with moderate to severe chronic plaque psoriasis provided a younger population with fewer comorbidities and concomitant medications, and as such, is also a sensitive and appropriate model to detect clinically meaningful differences in efficacy between ABP 501 and adalimumab, if such differences exist. Clinical equivalence between ABP 501 and adalimumab was confirmed and the efficacy results are considered predictive of similar efficacy in all other dermatologic conditions of use for which ABP 501 licensure is sought.

Given that the efficacy of ABP 501 and adalimumab was found to be similar in the respective studies conducted in rheumatoid arthritis and plaque psoriasis populations, in addition to the highly similar analytical and functional characteristics and PK similarity between ABP 501 and adalimumab, ABP 501 is expected to exhibit similar efficacy in all conditions of use for which ABP 501 licensure is sought.

## 6.6 Extrapolation Summary

The totality of evidence indicates that ABP 501 would be expected to be as safe and efficacious as adalimumab in all conditions of use for which approval is sought.

Specifically:

- A comprehensive functional similarity assessment demonstrated similarity between ABP 501 and adalimumab in all mechanisms of action including those possibly relevant to efficacy in inflammatory bowel disease.
- Equivalent PK profiles in healthy subjects as well as similar steady-state drug levels in the studied and extrapolated patient populations are predictive of equivalent PK in all indications.
- Similar immunogenicity rates between ABP 501 and adalimumab were demonstrated in patients with and without the use of methotrexate, thus representing similarity across a range of immunosuppression.
- ABP 501 and adalimumab have shown safety and efficacy profiles similar to previously reported data for adalimumab, and ABP 501 is similar to adalimumab in the studies presented here, inclusive of younger plaque psoriasis patients and rheumatoid arthritis patients with concomitant methotrexate.
- Based on all of the factors assessed above, ABP 501 is expected to retain the same safety and efficacy profile as adalimumab in all indications sought.

## 7. CONCLUSION

This document summarizes the comprehensive results of analytical similarity, nonclinical, and clinical studies to establish the biosimilarity of ABP 501 to adalimumab and support the extrapolation across all indications for which Amgen is seeking licensure. The ABP 501 analytical program demonstrated a high level of analytical similarity between ABP 501 and adalimumab. The program included assessments of multiple TNFα functions that are common to all indications of use for adalimumab and for which Amgen is seeking licensure. Additional assessments which may be important to the mechanisms of action in specific indications also demonstrated a high level of similarity.

Following the analytical and nonclinical similarity assessments, Amgen conducted a randomized, single-blind, single-dose, 3-arm (ABP 501 vs adalimumab [US] vs adalimumab (EU]) study in healthy male and female subjects. The study demonstrated PK similarity between ABP 501 and adalimumab (US), as well as PK similarity between ABP 501 and adalimumab (EU) and between adalimumab (US) and adalimumab (EU). The results from this PK similarity study combined with analytical similarity data scientifically justify the relevance of comparative clinical data between ABP 501 and adalimumab (EU) and established the requisite scientific bridge between adalimumab (US) and adalimumab (EU).

Clinical similarity was then established in 2 randomized, double-blind, active comparator-controlled clinical trials (rheumatoid arthritis Study 20120262 and plaque psoriasis Study 20120263) to complete the totality of evidence evaluation.

Amgen has met the requirement for establishing biosimilarity to the US reference product, specifically:

1. ABP 501 is highly similar to adalimumab notwithstanding minor differences in clinically inactive components.

and

2. There are no clinically meaningful differences between ABP 501 and adalimumab in terms of the safety, efficacy, and immunogenicity.

This conclusion supports the approval of ABP 501 as a biosimilar to adalimumab (US). Additionally, Amgen has provided evidence to support the approval of ABP 501 in all of the adalimumab indications for which licensure is sought.

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## Appendix 1. Supporting Method Descriptions and Data

This appendix provides supporting method descriptions and graphical data for a subset of the structural, purity, and functional methods. For the full results of all methods performed during the analytical similarity assessment, please refer to Section 3.2 in the briefing document.

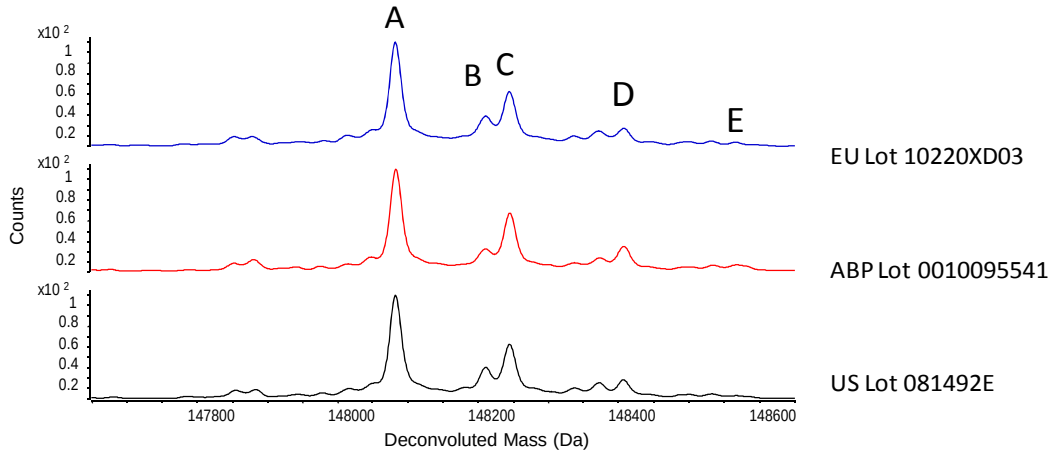
## 9. ANALYTICAL CHARACTERIZATION DATA

### 9.1 Primary Structure

**Intact Molecular Mass**

The intact molecular mass of ABP 501 and adalimumab was determined by electrospray ionization-time of flight-mass spectrometer (ESI-TOF-MS) analysis. Samples were separated from buffer components and introduced to the mass spectrometer by reverse-phase high performance liquid chromatography (RP-HPLC). The resulting summed ion spectra were deconvoluted to produce molecular mass profiles.

**Figure 51. Intact Molecular Mass for Adalimumab (EU), ABP 501, and Adalimumab (US)**

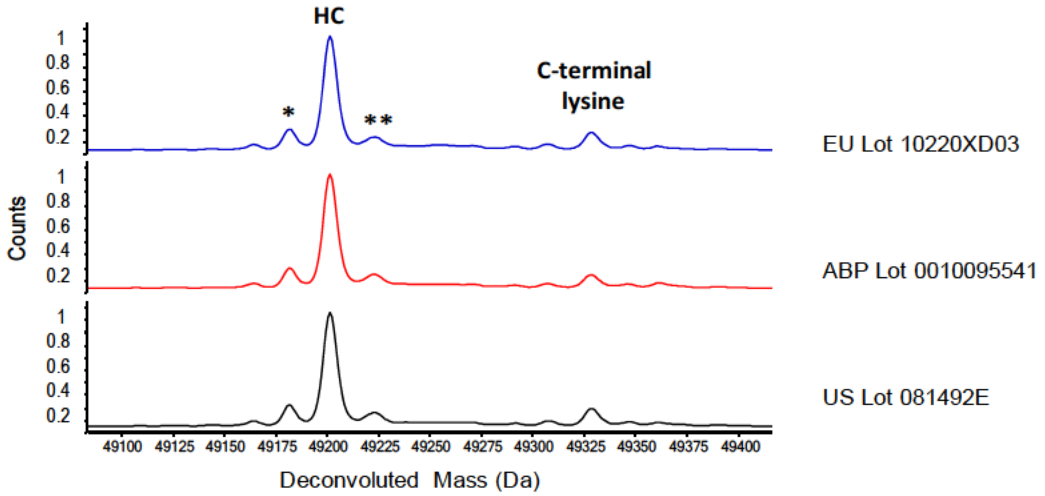



A = A2G0F:A2G0F; B = A2G0F:A2G0F+K*; C = A2G0F:A2G1F; D = A2G1F:A2G1F or A2G0F:A2G2F; E = A2G1F:A2G2F.

**Reduced and Deglycosylated Molecular Masses of Heavy Chain and Light Chain**

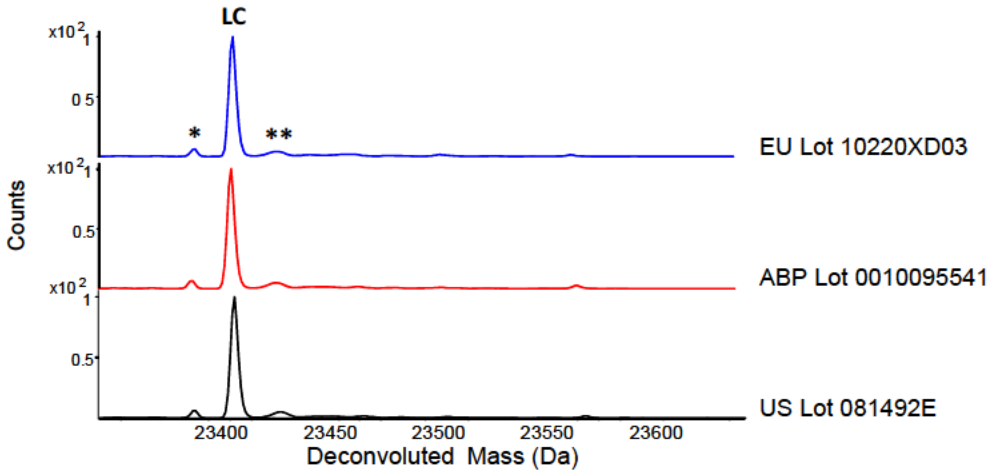
The molecular masses of reduced and deglycosylated ABP 501 and adalimumab were evaluated using ESI-TOF-MS to provide further assurance that the polypeptide compositions are as expected. Samples were treated with PNGase F to remove N-linked glycans, subsequently denatured, and the disulfides reduced. The PNGase F-treated and disulfide-reduced samples were separated from buffer components and introduced to the mass spectrometer via reversed-phase chromatography. Summed ion spectra were deconvoluted to produce molecular mass profiles which were compared with theoretical mass values.

**Figure 52. Comparison of Reduced and Deglycosylated Heavy Chain Mass Profiles for Adalimumab (EU), ABP 501, and Adalimumab (US)**




* Ionization artifact as a result of water loss (-18 Da)
** Ionization artifact as a result of sodium adduct (+22 Da)

**Figure 53. Comparison of Reduced and Deglycosylated Light Chain Mass Profiles for Adalimumab (EU), ABP 501, and Adalimumab (US)**




* Ionization artifact as a result of water loss (-18 Da)
** Ionization artifact as a result of sodium adduct (+22 Da

## Reduced Peptide Map

Peptide map analysis was conducted by enzymatic digestion with trypsin, followed by reduction with dithiothreitol and alkylation with sodium iodoacetic acid. The resulting cleavage fragments were separated by reversed phase ultra-performance liquid chromatography (UPLC) using an increasing gradient of acetonitrile in water. The eluted peaks were detected by ultraviolet (UV) absorbance (214 nm). The peptides were identified by on-line mass spectrometry.

**Figure 54. Reduced Tryptic Peptide Map for Adalimumab (EU), ABP 501, and Adalimumab (US)**

(A) Time: 0 to 80 minutes

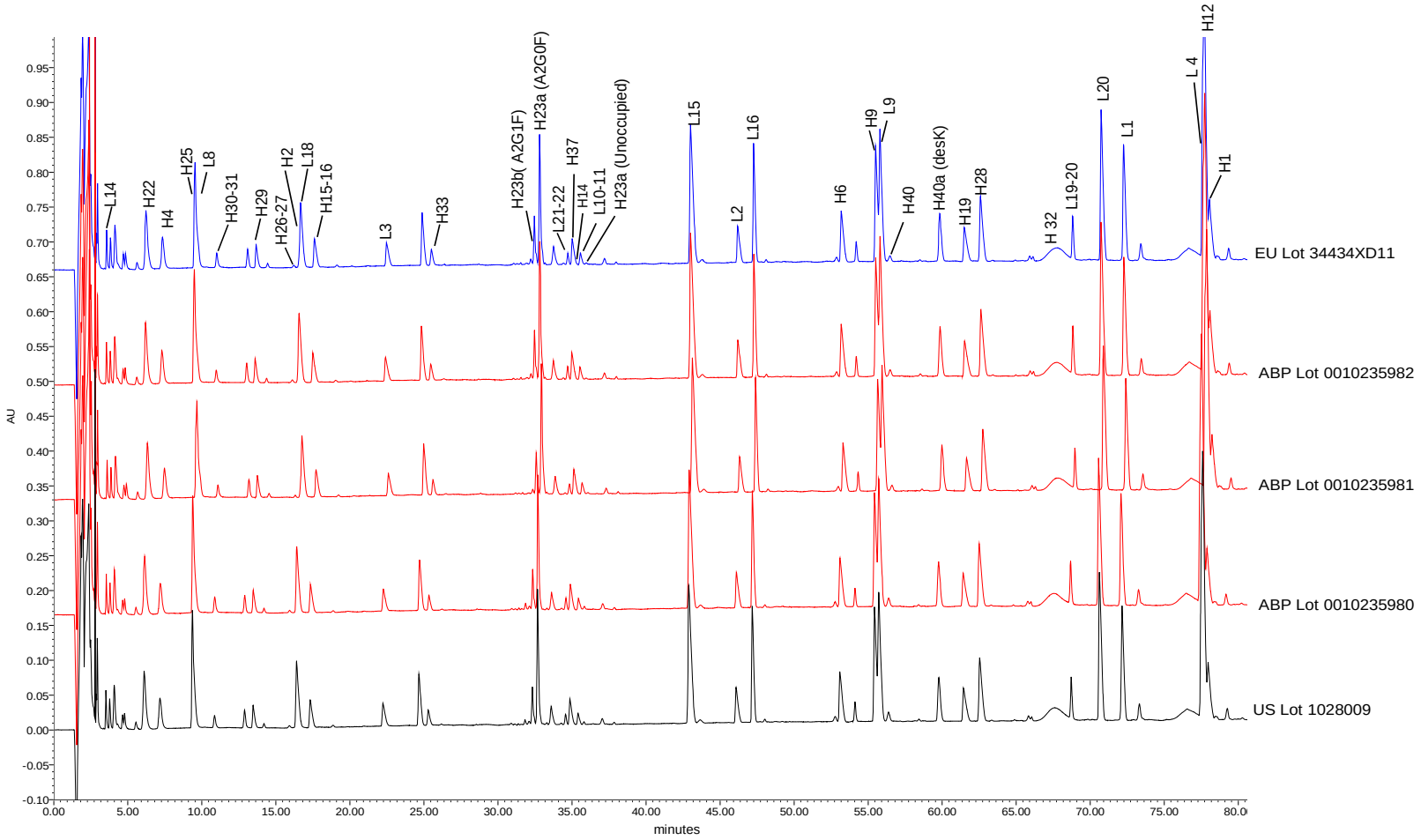
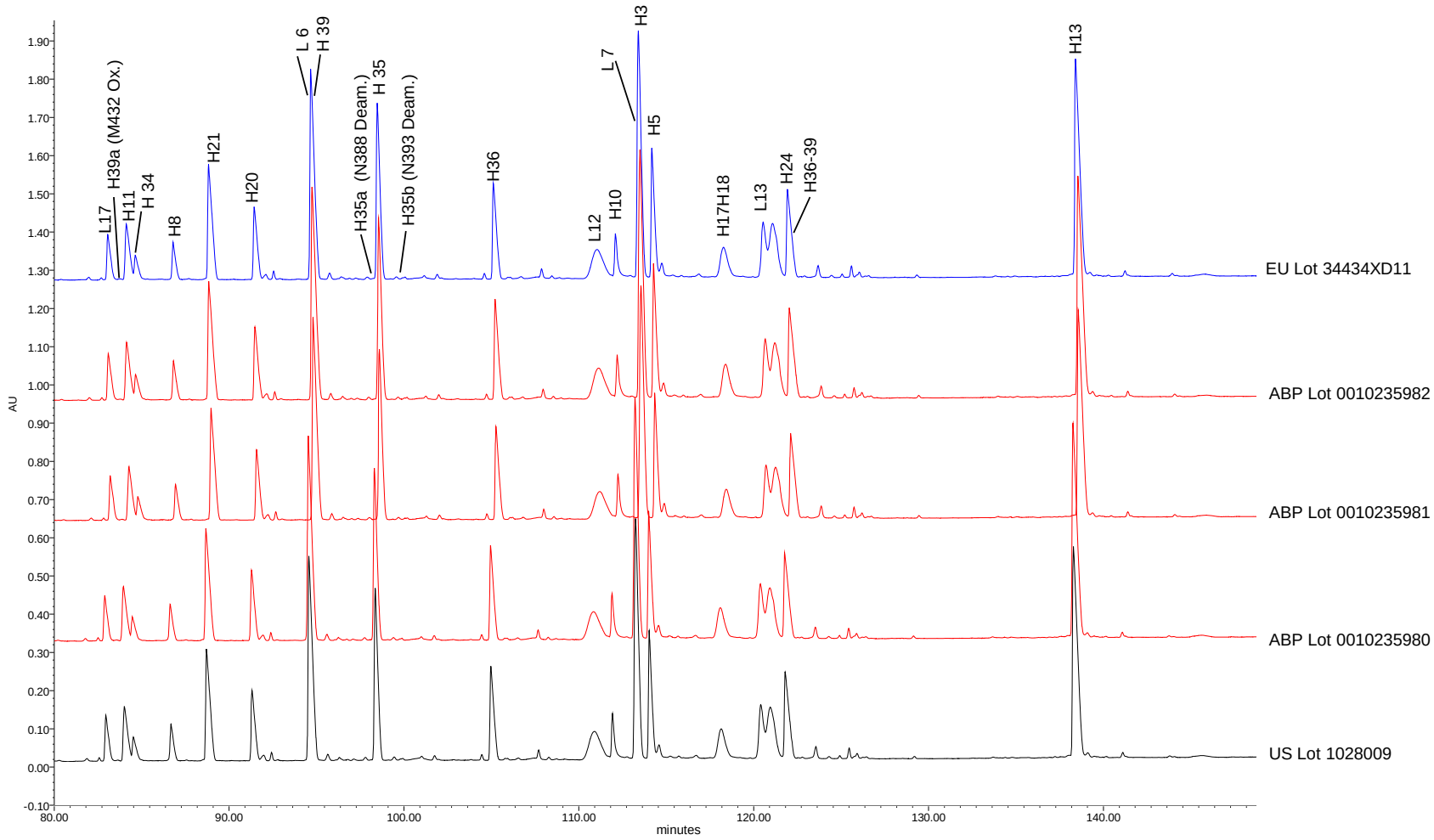


**Figure 54. Reduced Tryptic Peptide Map for Adalimumab (EU), ABP 501, and Adalimumab (US)**

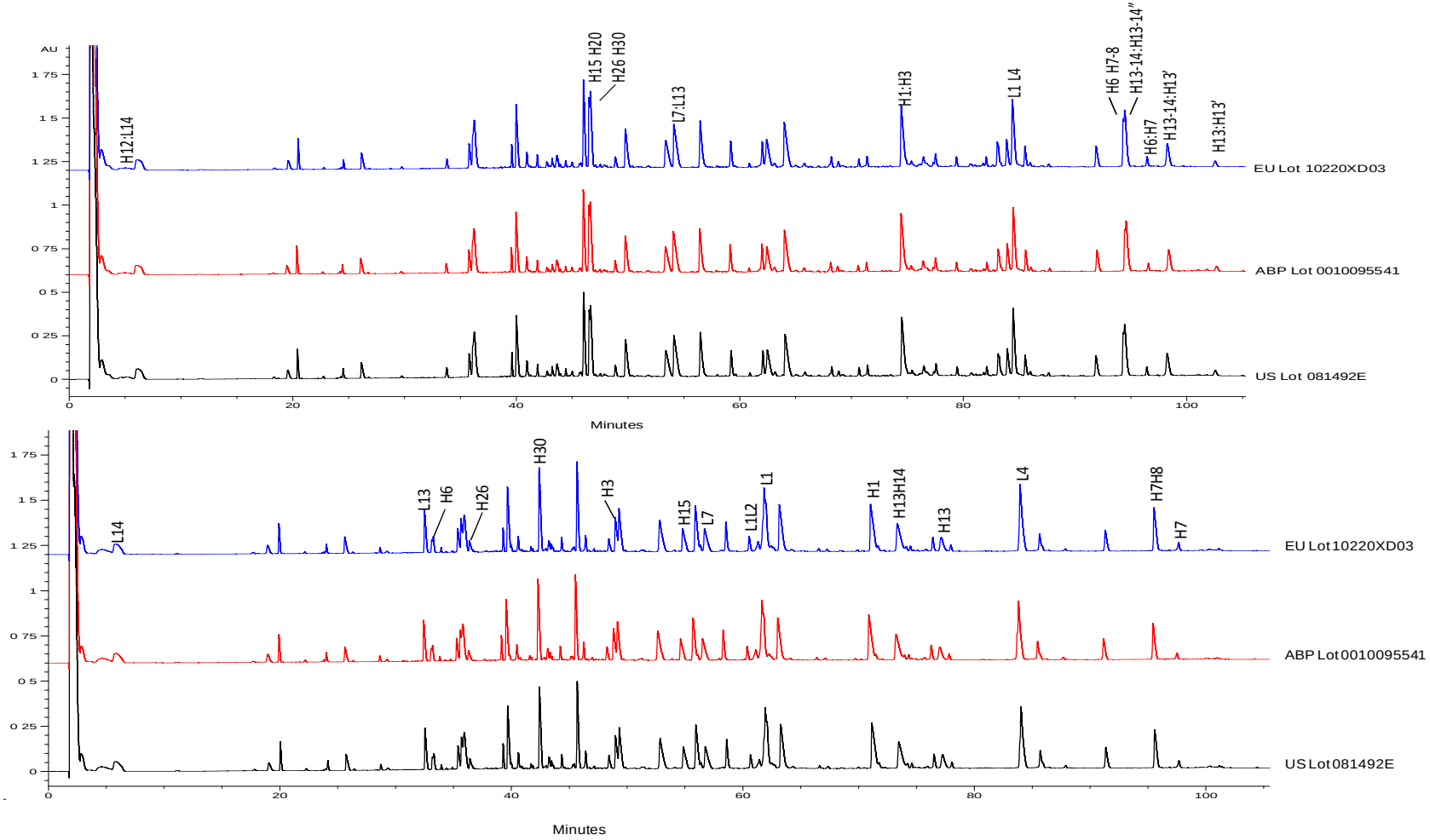
(B) Time: 80 to 145 minutes



**Disulfide Structure – Non-reduced Peptide Map**

Samples were digested with the endoprotease Lys-C under denaturing, but non-reducing conditions. The resulting peptides were analyzed by RP- HPLC using an increasing gradient of acetonitrile in water with UV light detection at 214 nm. The peptides containing disulfide bonds were identified by comparing peptides generated under reducing and non-reducing conditions. Confirmation of peptide identity was achieved using an HPLC system coupled through an electrospray interface to a high-resolution mass spectrometer, allowing determination of the molecular mass of each peptide.

**Figure 55. Non-reduced (Top) and Reduced (Bottom) Lys-C Maps for Adalimumab (EU), ABP 501, and Adalimumab (US)**

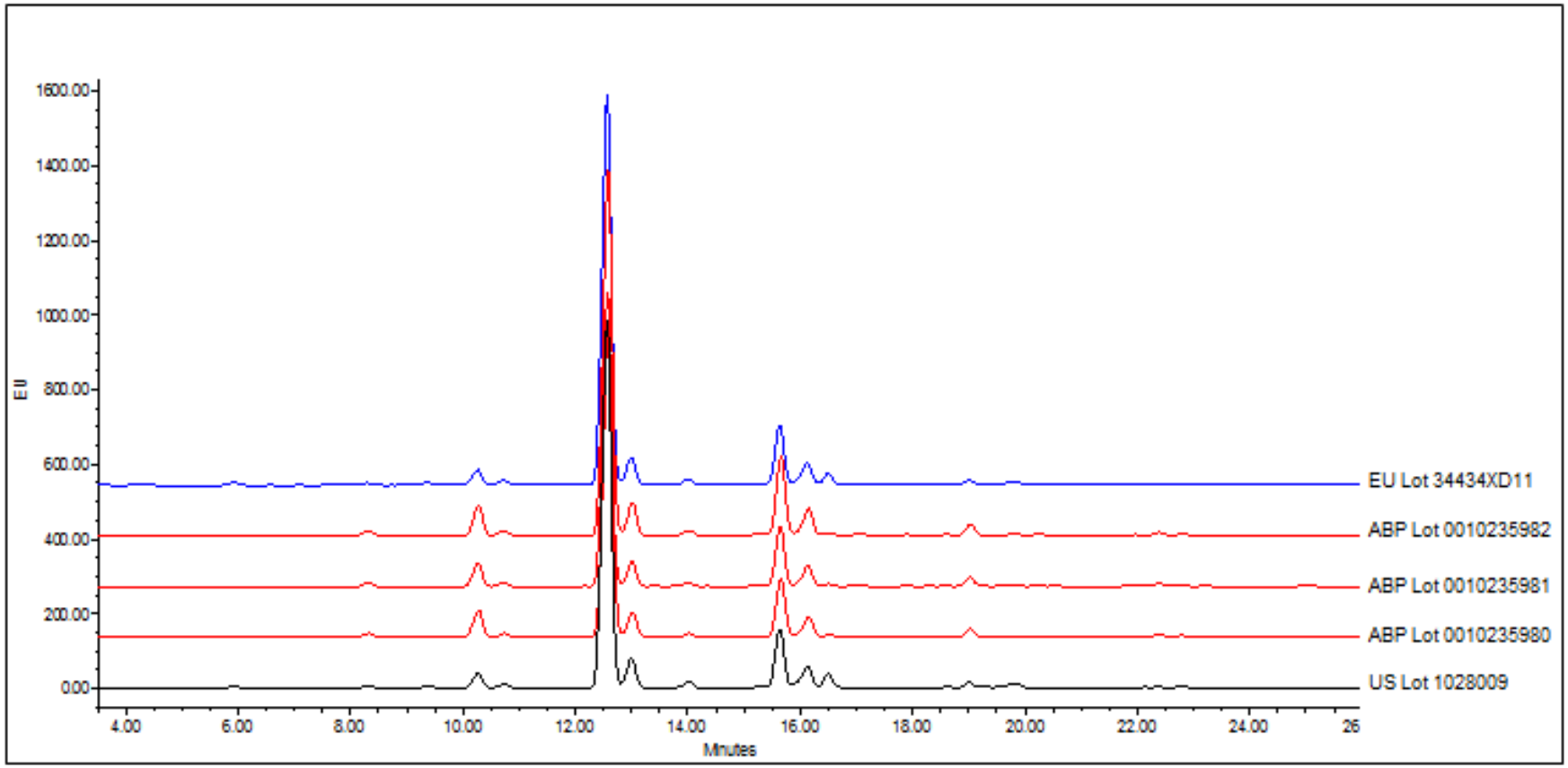



Only peptides involved in disulfide pairing are labeled.

## Glycan Map

N-linked glycan profiles of ABP 501, adalimumab (US), and adalimumab (EU) are evaluated by hydrophilic interaction liquid chromatography (HILIC) HPLC glycan map analysis. This procedure involves releasing the N-linked glycans with PNGase F. The released oligosaccharides are derivatized with the fluorescent label 2-aminobenzoic acid (2-AA) at the reducing terminal N-acetylglucosamine (GlcNAc). The labeled oligosaccharides are separated by HILIC HPLC with an increasing gradient of ammonium formate in water and detected by fluorescence.

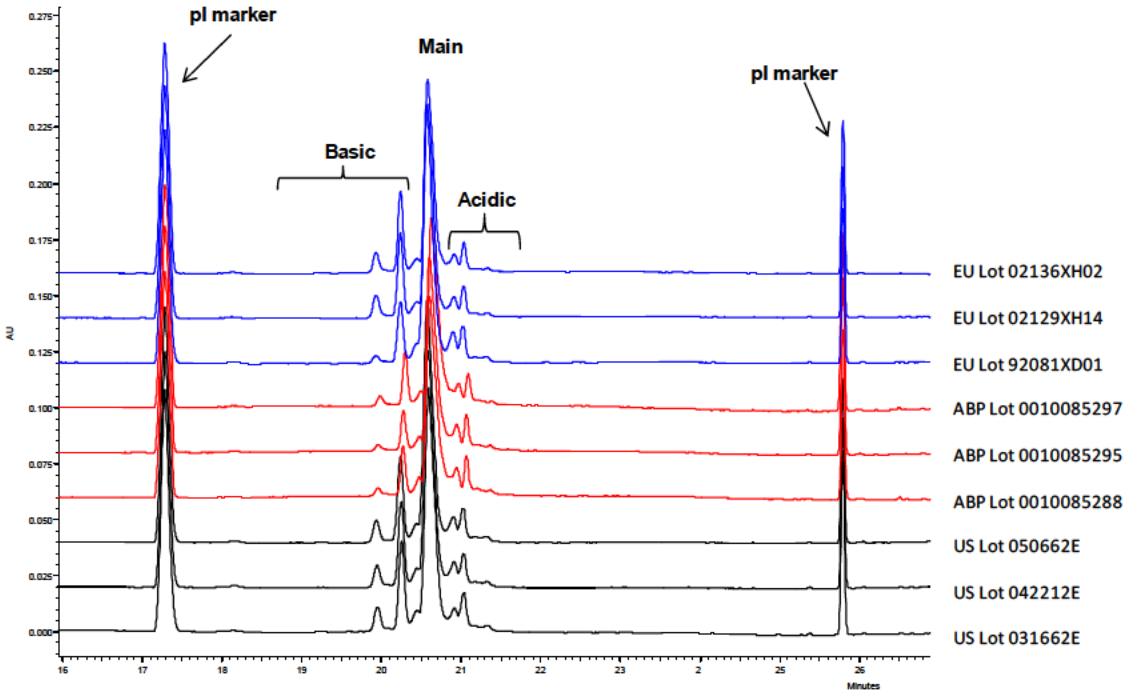
**Figure 56. HILIC Glycan Map for Adalimumab (EU), ABP 501, and Adalimumab (US)**



**Isoelectric Point - Capillary Isoelectric Focusing (cIEF)**

cIEF was performed by electrophoresis of proteins through a pH gradient in a capillary. cIEF was performed on a high resolution capillary electrophoresis separation instrument equipped with a neutral-coated capillary. The protein migrated through the pH gradient until it reached the pH equal to its isoelectric point (pI) and was then mobilized and detected by UV absorbance (280 nm) as it passed through a detection window in the capillary. To obtain the pI of the main peak, a linear regression between the 2 pI marker peaks was used.

**Figure 57. Comparison of cIEF Profiles for Adalimumab (EU), ABP 501, and Adalimumab (US)**




## 9.2 Higher Order Structure

**Fourier-transform Infrared (FTIR) Spectroscopy**

The FTIR measurements of ABP 501 and adalimumab were performed side-by-side at room temperature using an FTIR spectrometer. The second derivative spectrum was calculated using a 9 point smoothing of the original spectra.

**Figure 58. Second Derivative FTIR Spectra Comparing ABP 501 and Adalimumab (US)**

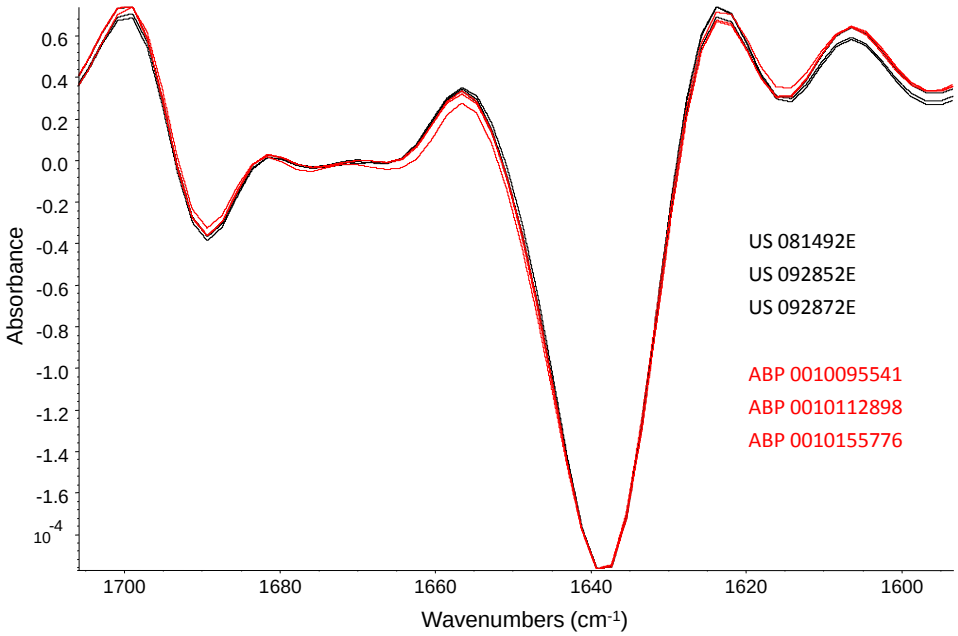
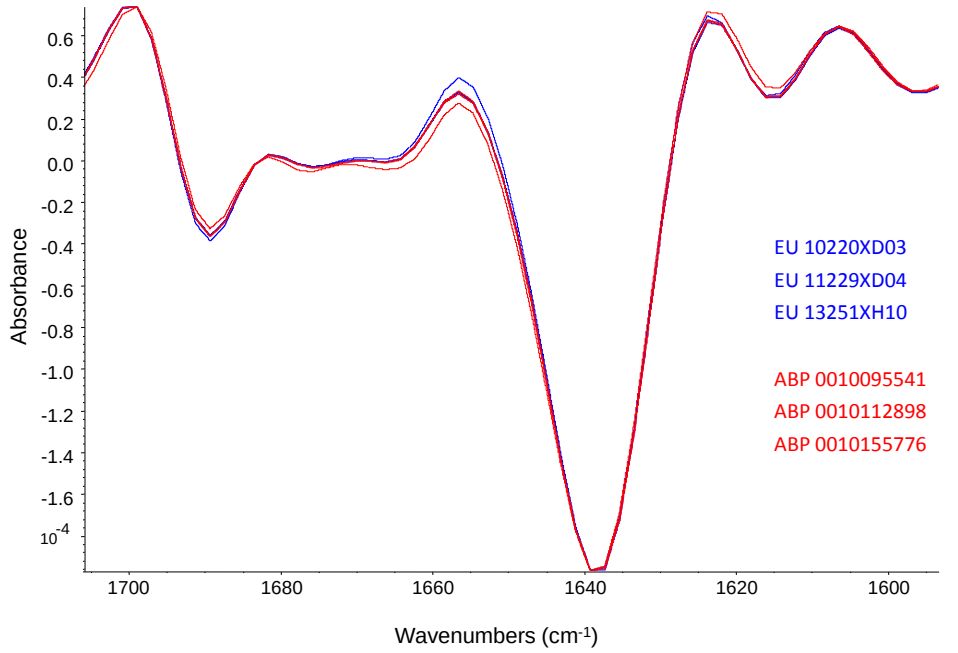



**Figure 59. Second Derivative FTIR Spectra Comparing ABP 501 and Adalimumab (EU)**




## Near Ultraviolet Circular Dichroism (UV CD) Spectroscopy

The near UV CD spectra of the samples were generated for side-by-side analysis on a spectropolarimeter at ambient temperature using cuvettes with a pathlength of 1 cm. The spectra are corrected for concentration and contributions from the buffer, and are reported as CD Ellipticity.

**Figure 60. Near UV CD Spectra Comparing ABP 501 and Adalimumab (US)**

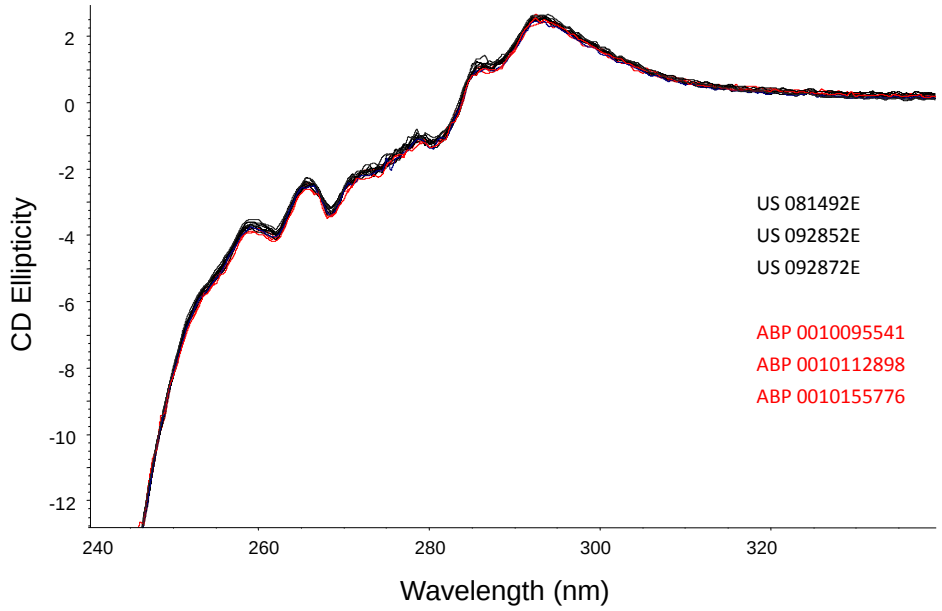
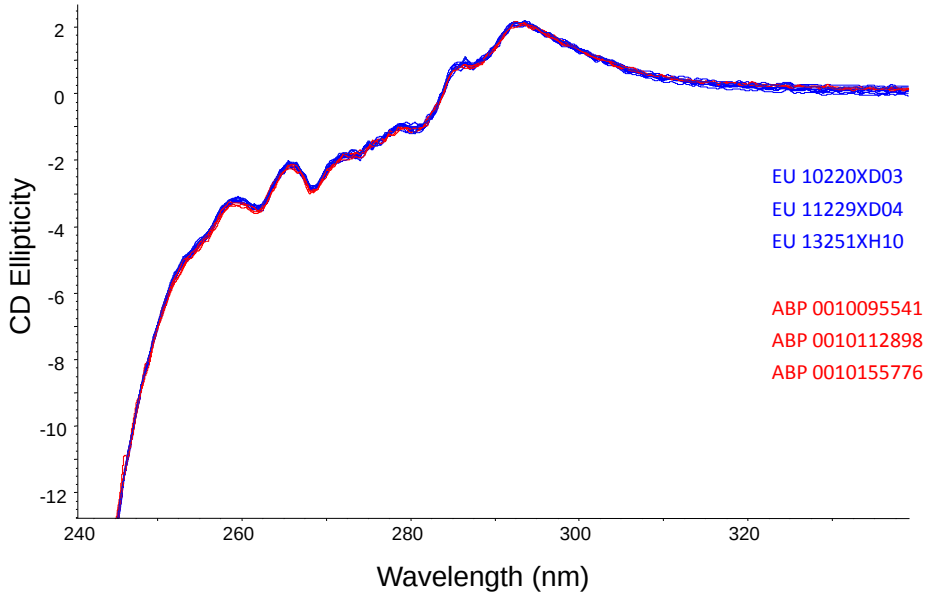


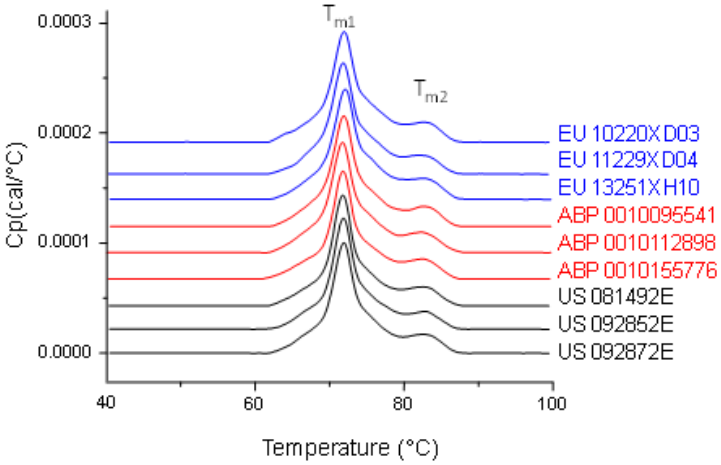

**Figure 61. Near UV CD Spectra Comparing ABP 501 and Adalimumab (EU)**




## Differential Scanning Calorimetry (DSC)

The thermal stability of the samples was assessed side-by-side by DSC using a system in which temperature differences between the reference and sample cell are continuously measured, and calibrated to power units. The unfolding of the protein molecules appears as an endothermic transition on the DSC thermogram and can be characterized by the thermal melting temperatures ($T_m$). The protein concentrations used in the DSC experiments are approximately 0.5 mg/mL and obtained by diluting the original samples in adalimumab drug product buffer. Triplicate tests were performed on all samples, and the results are reported as the mean from the multiple determinations.

**Figure 62. DSC Scans of Adalimumab (EU), ABP 501, and Adalimumab (US)**



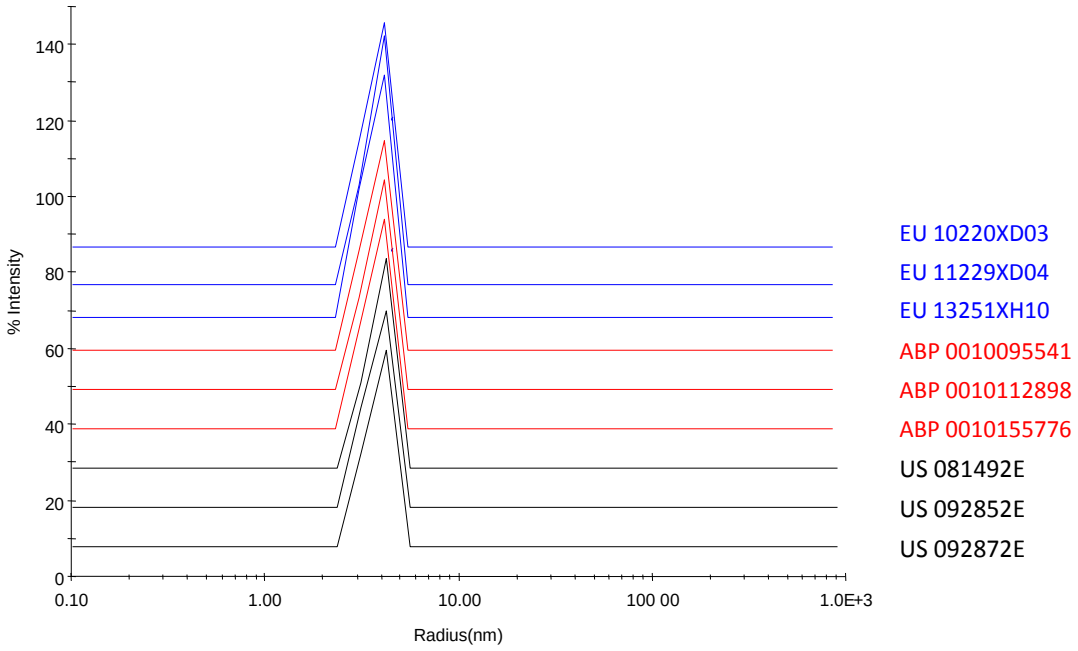

## 9.3 Particles and Aggregates

### Submicron Particle Analysis

**Dynamic Light Scattering (DLS)**

DLS measures the time scale of light intensity fluctuations to determine the particle size and the distribution of particle sizes in the nanometer to micron size range. Particle size distributions of the ABP 501 and adalimumab drug product samples were determined on a DLS instrument at 25°C. The samples were measured after dilution in adalimumab drug product buffer to approximately 1 mg/mL, and each sample was analyzed in 3 replicate tests side-by-side. The viscosity based on buffer composition was used for calculating the size distribution.

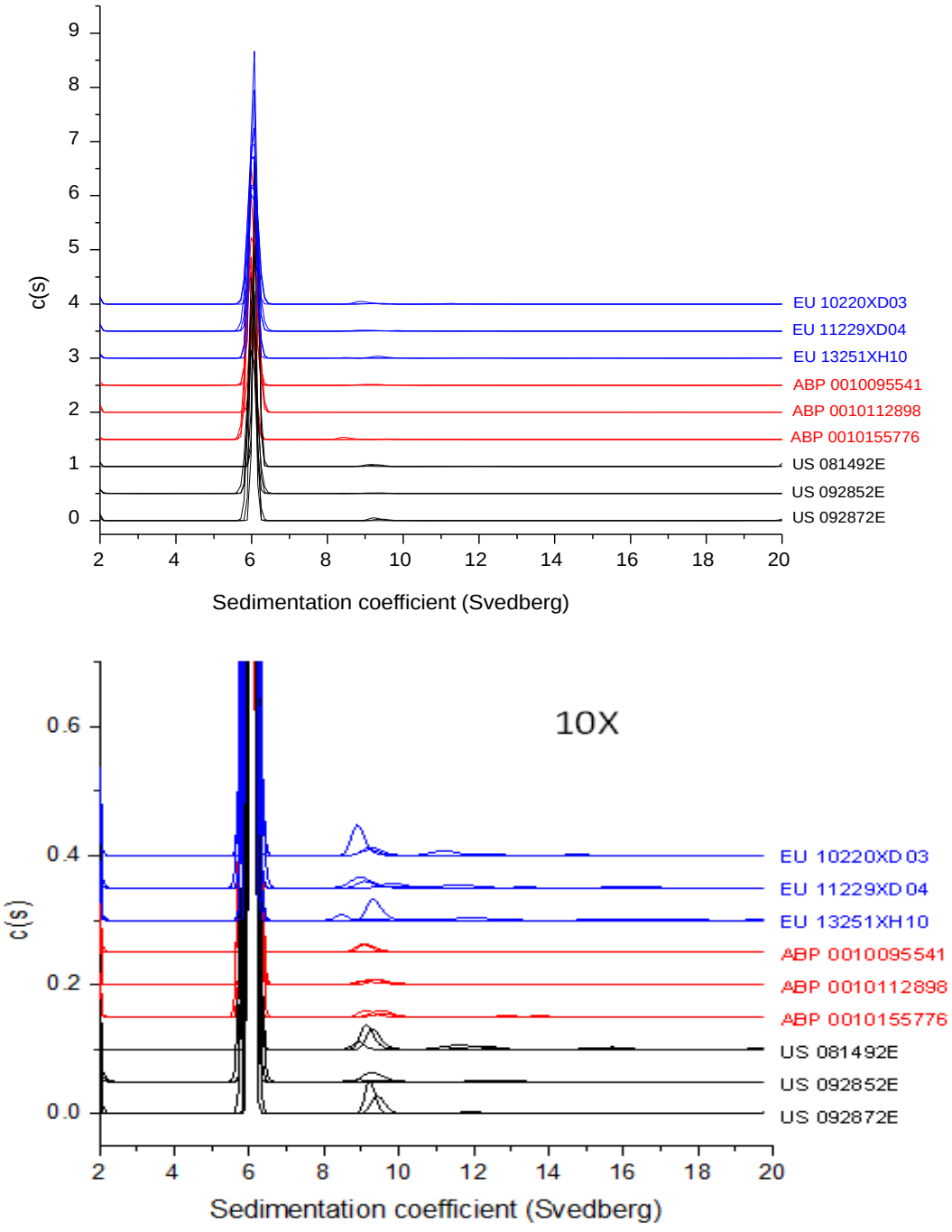
**Figure 63. Dynamic Light Scattering Size Distribution Profiles for Adalimumab (EU), ABP 501, and Adalimumab (US)**



## Analytical Ultracentrifugation Sedimentation Velocity (AUC-SV)

ABP 501 and adalimumab samples were diluted to approximately 0.5 mg/mL in adalimumab drug product buffer before measurements by AUC-SV. The sedimentation velocity experiments were performed at 45,000 rpm, followed by absorbance at 280 nm. Triplicate measurements were carried out for each sample, and results were reported as the mean from the multiple determinations.

**Figure 64. AUC-SV Profiles for Adalimumab (EU), ABP 501, and Adalimumab (US)**




Vertical axis – sedimentation coefficient distribution
Horizontal axis – species separated based on sedimentation coefficients

**Size Exclusion High Performance Liquid Chromatography with Light Scattering Detection (SE-HPLC-LS)**

The SE-HPLC-LS method is capable of detecting high molecular weight (HMW) species (multimer and aggregate). Results were expressed as the molar mass of individual peaks from monomer through HMW species. The same SE-HPLC-LS method was employed coupled with a multi-angle light scattering (MALS) detector, a refractive index (RI) detector, and a UV detector with wavelength set at 280 nm. Samples were injected neat into the system at a load of approximately 280 μg. For the molar mass calculation, an RI increment value of 0.185 (mL/g) was used. Triplicate measurements were carried out for each sample.

**Figure 65. SE-HPLC-LS - ABP 501 and Adalimumab (US)**

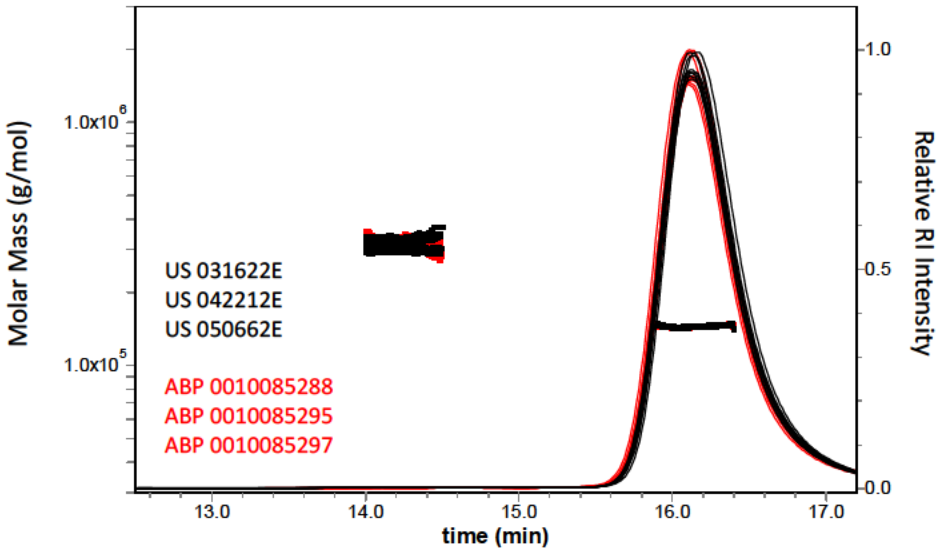
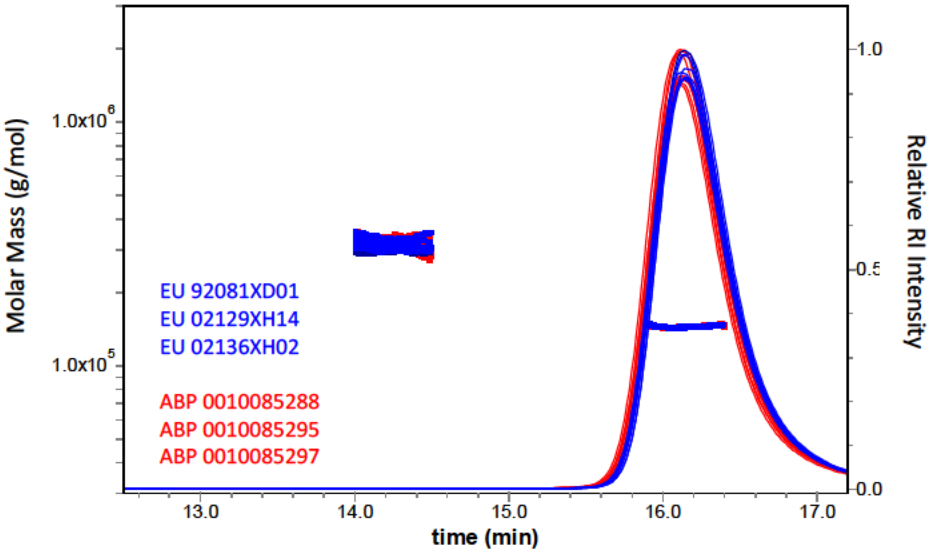



**Figure 66. SE-HPLC-LS - ABP 501 and Adalimumab (EU)**



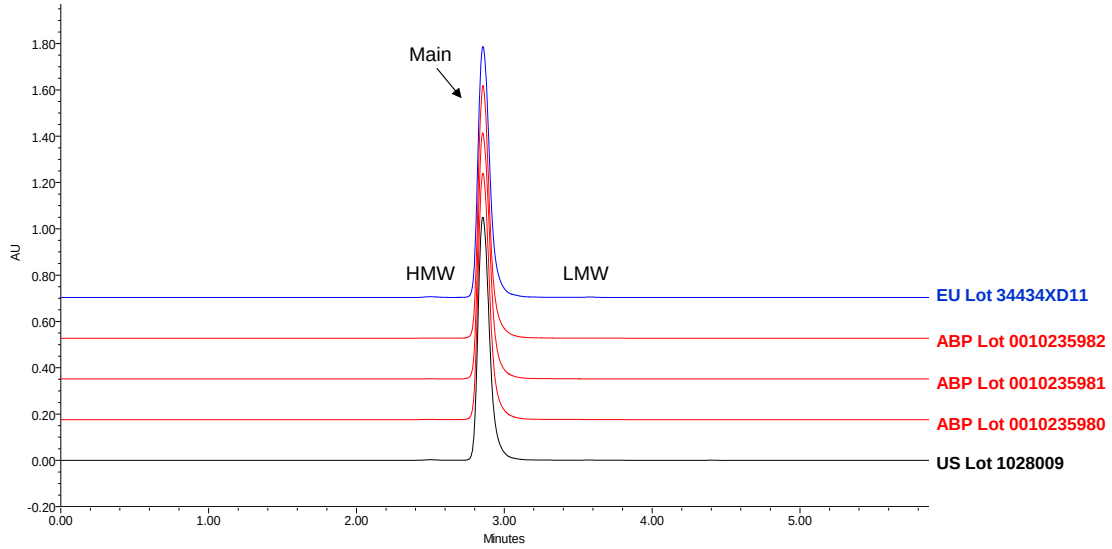
## 9.4 Product-related Substances and Impurities

**Size Exclusion – High Performance Liquid Chromatography (SE-HPLC)**

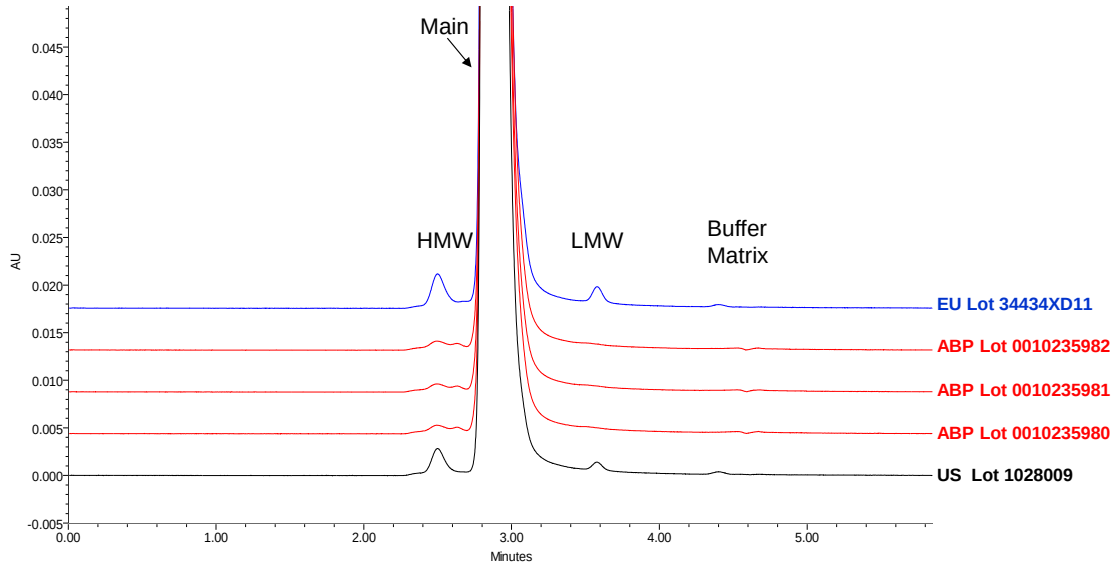
This SE-HPLC procedure is used to assess the purity of ABP 501. SE-HPLC separates proteins based on their hydrodynamic volume. The procedure is suitable for quantifying the level of low molecular weight species (LMW), the main peak, and the HMW species present.

**Figure 67. SE-HPLC Profiles for Adalimumab (EU), ABP 501, and Adalimumab (US)**

**Full View**




**Expanded View**

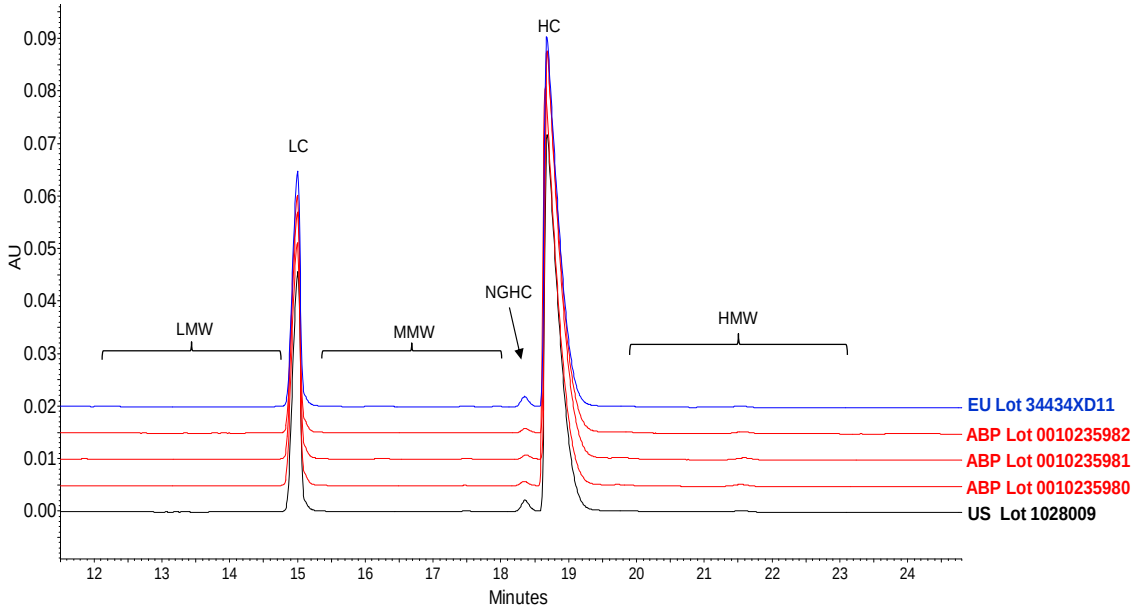


## Reduced Capillary Electrophoresis – Sodium Dodecyl Sulfate (rCE-SDS)

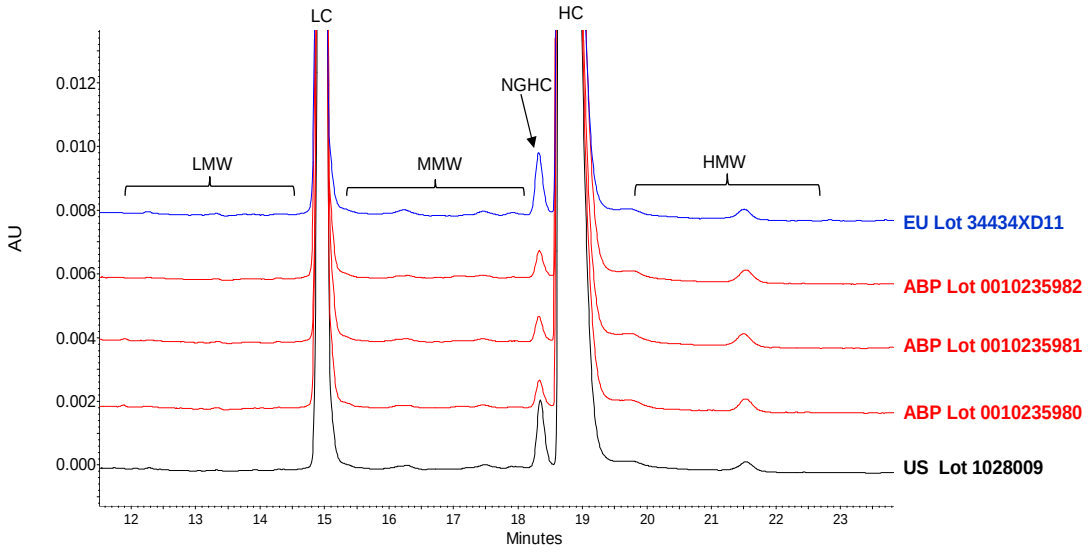
The rCE-SDS procedure is used to monitor purity, percent main (light chain [LC] + heavy chain [HC]) and percent total clipped species. ABP 501 is reduced using β–mercaptoethanol and denatured with SDS. The reduced denatured proteins are separated based on hydrodynamic size where smaller size proteins migrate faster and larger size protein migrate slower.

**Figure 68. Comparison of Adalimumab (EU), ABP 501, and Adalimumab (US) rCE-SDS Profiles**

**Full View**




**Expanded View**

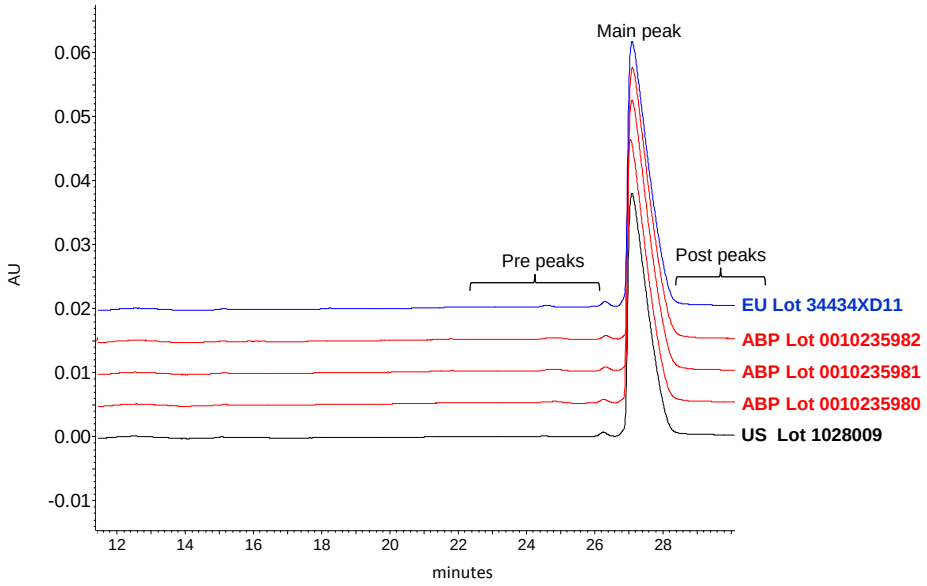


## Non-reduced Capillary Electrophoresis – Sodium Dodecyl Sulfate (nrCE-SDS)

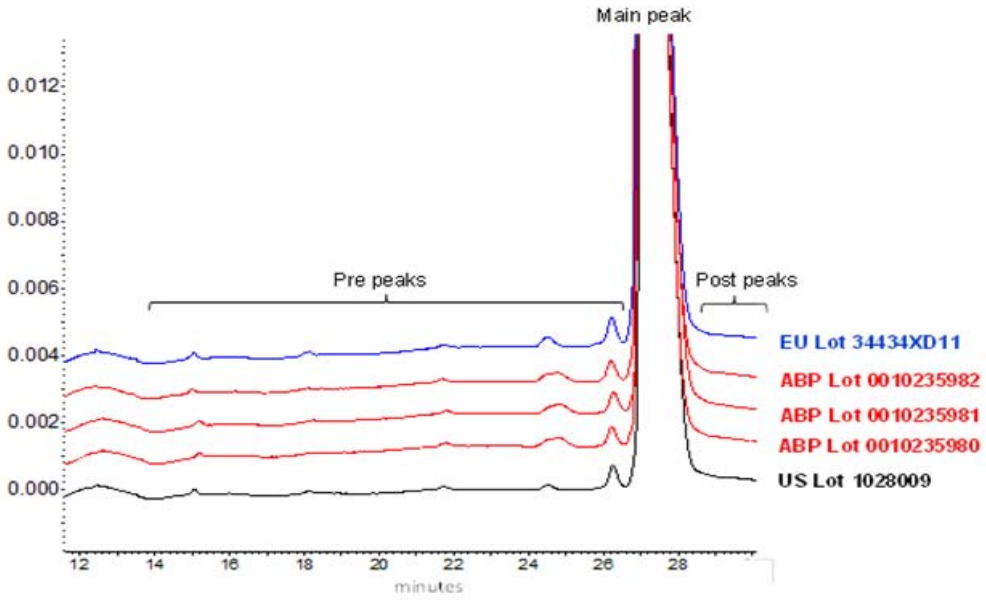
CE-SDS can also be performed under non-reducing conditions in order to evaluate the presence of non-monomeric species. This technique is performed under denaturing conditions to unfold the protein and disrupt non-covalent associations, and is particularly useful for detection of partial molecule species (eg, those lacking 1 or more of the 2 LC and 2 HC constituents expected of a monomeric antibody).

**Figure 69. Comparison of Adalimumab (EU), ABP 501, and Adalimumab (US) nrCE-SDS Profiles**

**Full View**




**Expanded View**

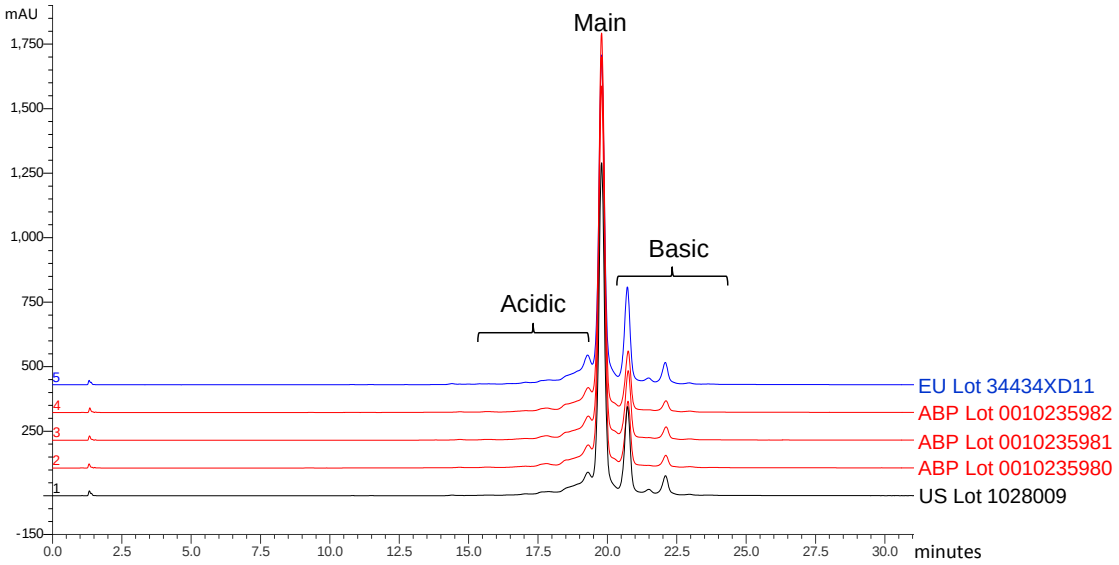


## Cation Exchange – High Performance Liquid Chromatography (CEX-HPLC)

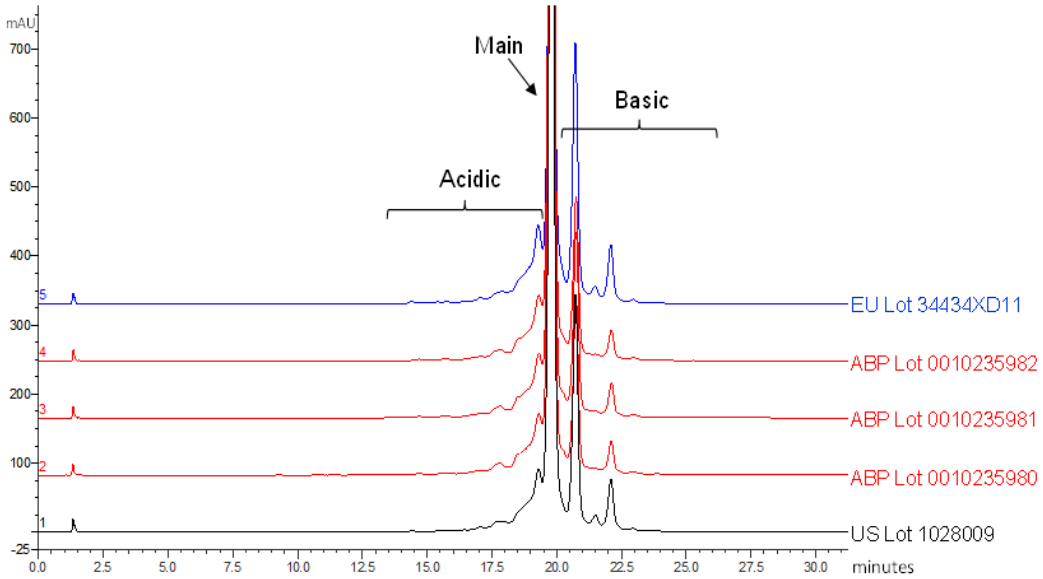
The CEX-HPLC procedure is used to assess the purity of ABP 501. CEX-HPLC separates proteins based on differences in their surface charges under appropriate pH conditions. CEX-HPLC separates ABP 501 chromatographically from minor product-related charged variants (isoforms) that are eluted using a salt gradient. Purity is determined by expressing the integrated area of the main the peak and the area of each charged isoform that elutes separately as a percentage of the total peak area.

**Figure 70. CEX-HPLC Profiles for Adalimumab (EU), ABP 501, and Adalimumab (US)**

### Full View




### Expanded View

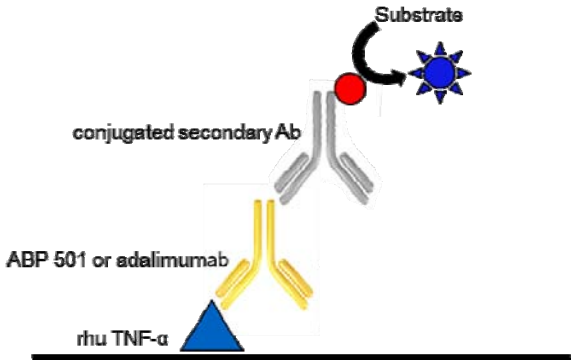


# 10. FUNCTIONAL ASSAY METHOD DESCRIPTIONS

## 10.1 Binding to Soluble TNFα

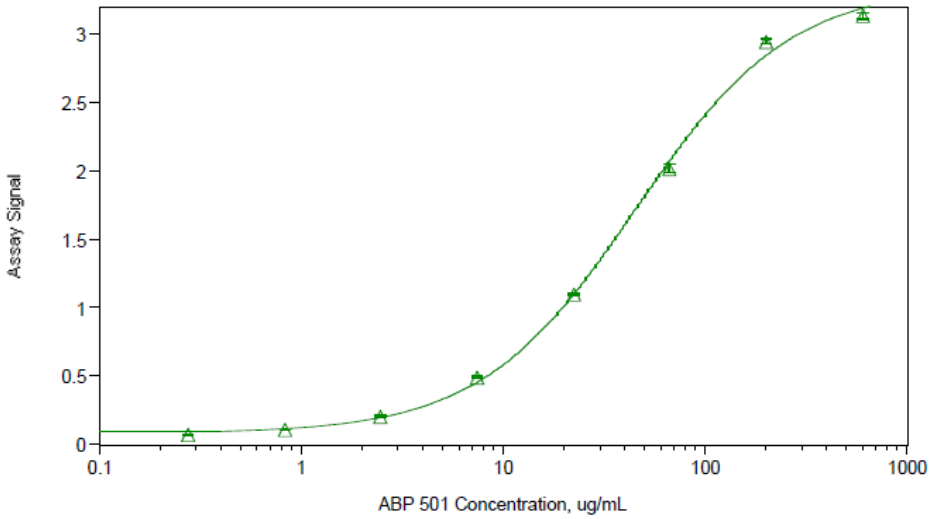
The soluble TNFα binding assay is based on a solid phase enzyme-linked immunosorbent assay (ELISA), as depicted in Figure 71. Recombinant human soluble TNFα is coated onto the wells of a microtiter ELISA plate. A dose titration of ABP 501 or adalimumab is applied as a test sample, and binding is detected using an anti-human IgG conjugated to horseradish peroxidase. When a substrate is added, the color change is proportional to the amount of ABP 501 or adalimumab bound to soluble TNFα. Graphing software is used to perform a 4-parameter data analysis and a constrained model curve fit to the data. Relative receptor binding activities are calculated based on the ratio of $ED_{50}$ values (the effective dose at which 50% inhibition is observed) of the reference standard curve relative to the test sample. A representative dose-response curve for the ABP 501 reference standard is provided in Figure 72.

**Figure 71. Schematic of TNF Binding ELISA**




Ab = antibody; ELISA = enzyme-linked immunosorbent assay; rhuTNF-α = recombinant human tumor necrosis factor alpha.

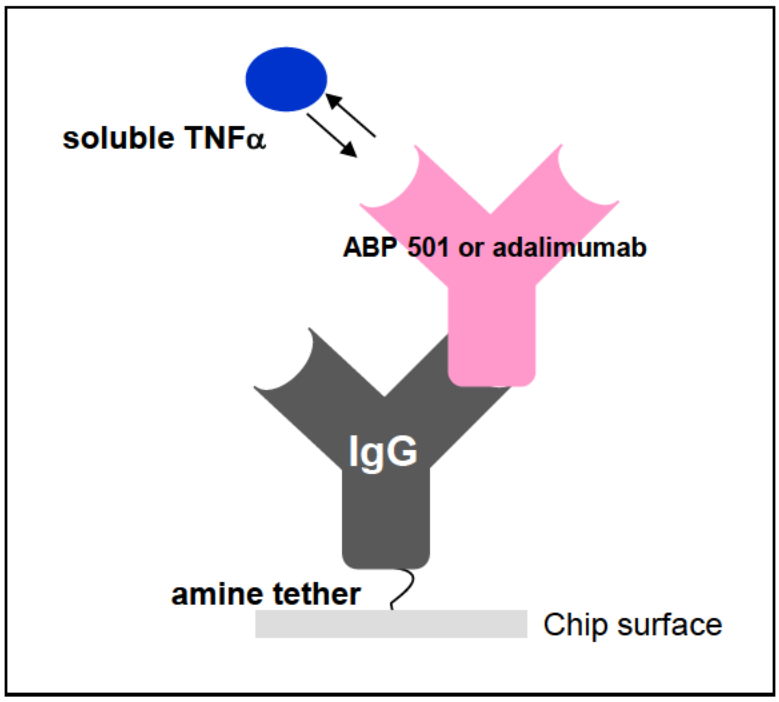
**Figure 72. Representative Dose-response Curve of ABP 501 Reference Standard in the TNFα-binding ELISA assay**



### 10.2 Binding Kinetics to Soluble TNFα

Surface plasmon resonance (Biacore) analysis was used to determine the association and dissociation rate constants ($k_a$, $k_d$), and dissociation equilibrium binding constant ($K_d$) for TNFα binding to ABP 501 and adalimumab. A goat anti-human IgG Fc-specific capture antibody was immobilized to the sensor chip allowing for subsequent capture of each human anti-TNFα monoclonal antibody. Binding of ABP 501 or adalimumab to TNFα was determined using "Single Cycle Kinetics" analysis with escalating concentrations of TNFα (0.18 to 60 nM), as represented in Figure 73. The double referenced data from the Single Cycle Kinetic run was fit locally to a 1:1 binding model with Biacore Kinetics software.

**Figure 73. Schematic of the Soluble TNFα Biacore Method**

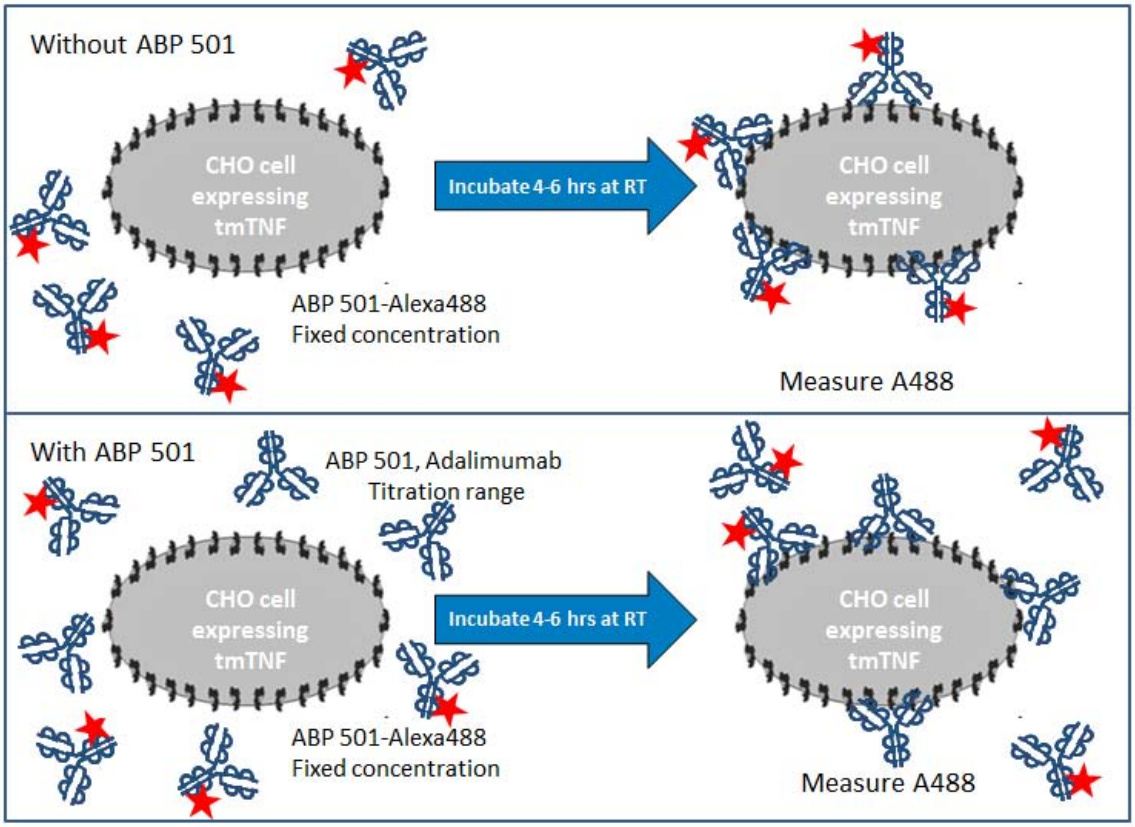



IgG = immunoglobulin class G; TNFα = tumor necrosis factor alpha.

### 10.3 Binding to Transmembrane TNFα

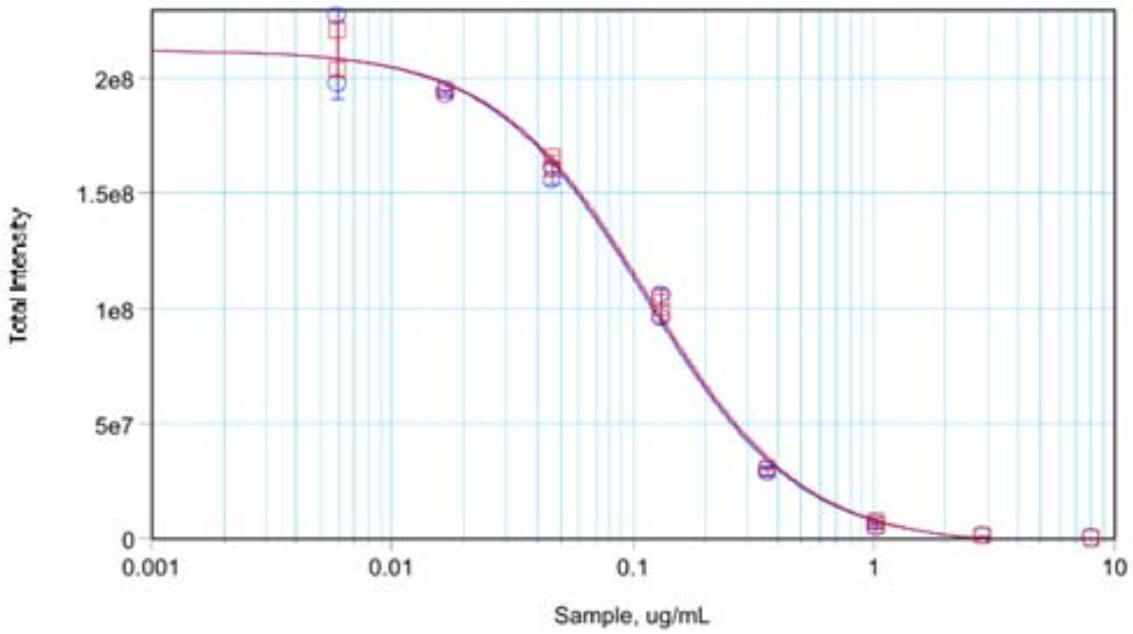
A cell-based competitive binding assay, as represented in Figure 74, was used to comparatively test binding to transmembrane TNFα. The method uses Chinese hamster ovary (CHO) cells expressing non-cleavable TNFα and Alexa 488 (A488)-labeled ABP 501. TNFα-expressing CHO cells were incubated with the labeled ABP 501 and with a dose titration of ABP 501 or adalimumab. Competitive binding was assessed by measuring A488 on an image cytometer. Binding of the test monoclonal antibodies to transmembrane TNFα is reflected in the decreased binding of the labeled ABP 501. Graphing software is used to fit the data using a 4 parameter logistic model, and parallelism of the samples is assessed. Then the sample $IC_{50}$, the concentration that produces 50% inhibition of the response, is calculated. The relative binding is calculated by comparing the $IC_{50}$ of the reference standard to that of the test sample. Representative dose-response curves for the ABP 501 reference standard and control are provided in Figure 75.

**Figure 74. Representation of the Competitive Transmembrane TNFα Binding Assay**




CHO = Chinese hamster ovary; RT = room temperature; tmTNF = transmembrane tumor necrosis factor.

**Figure 75. Representative Plot of ABP 501 Dose-response in a Competitive Transmembrane TNFα Binding Assay**

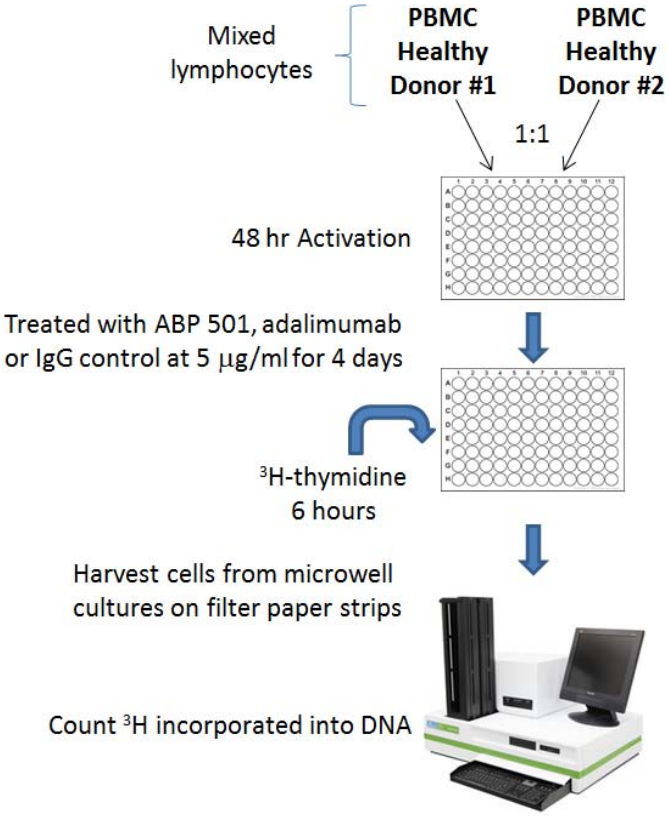



red = ABP 501 control sample; blue = ABP 501 reference standard sample.

### 10.4 Transmembrane TNFα Dependent Functional Assay: Inhibition of Proliferation in a Mixed Lymphocyte Reaction

A method was established to qualitatively test inhibition of proliferation in a mixed lymphocyte reaction (MLR) by ABP 501 as compared to adalimumab. In this assay, primary peripheral blood mononuclear cells (PBMCs) from 2 different healthy volunteers were used to establish an MLR (48 hours). The test samples, 5 μg/mL ABP 501 or adalimumab or a negative control IgG1, were added to the MLR and the culture was allowed to proliferate for an additional 4 days. Proliferation was assessed using radiolabeled nucleotide incorporation (during the final 6 hours). An overview of the MLR method protocol is shown in Figure 76. The method is intended to give a qualitative assessment of the ability to inhibit proliferation relative to a control IgG1.

**Figure 76. Schematic of the Mixed Lymphocyte Reaction Assay**



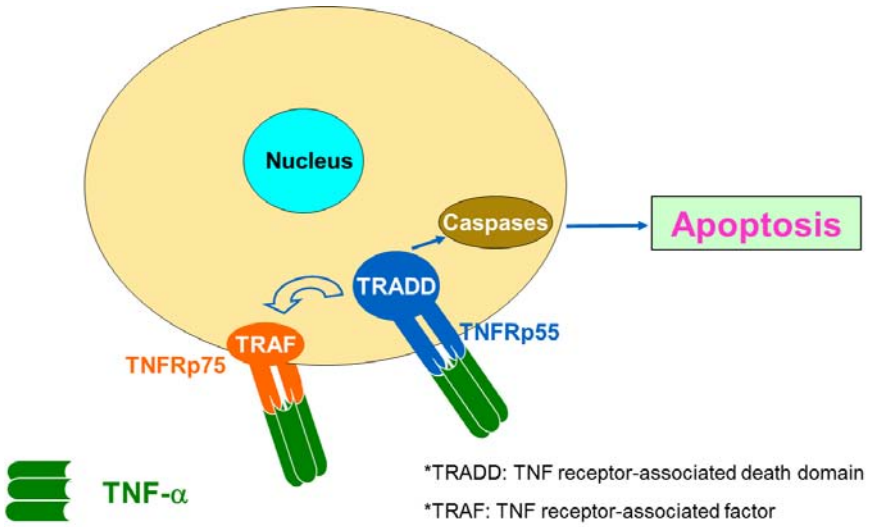

IgG = immunoglobulin class G; PBMC = peripheral blood mononuclear cell.

## 10.5 Apoptosis Inhibition Bioassay (Potency)

The inhibition of TNFα-induced apoptosis is used as the primary potency assay for ABP 501, and measures the ability of ABP 501 or adalimumab to inhibit soluble TNFα dependent apoptosis of the human monocytic U-937 cell line. TNFα induces U-937 cells to undergo apoptosis through caspase activation. A luminogenic substrate containing the DEVD amino acid sequence (Asp-Glu-Val-Asp) is recognized by these caspases and when cleaved, the luminescence generated is proportional to the amount of apoptosis in the cells. The principle of the biological assay is depicted in Figure 77. U-937 cells are stimulated with 3 ng/ml TNFα in the presence of a dose titration of ABP 501 or adalimumab, and resulting caspase activation is measured using the caspase-Glo3/7® reagent. A constrained curve fit model is applied to the data, and 4-parameter data analysis is used to generate the final results. In this analysis, ABP 501 and adalimumab relative potency was assessed using the $EC_{50}$ (effective concentration at which an inhibition of 50% of the maximal inhibition is observed) and reported as a percent of the activity of reference standard. A representative dose-response curve of ABP 501 and adalimumab is shown in Figure 78.

**Figure 77. Principle of ABP 501 Cell-based Apoptosis Inhibition Bioassay**

Panel A: In the absence of ABP 501




Panel B: In the presence of ABP 501

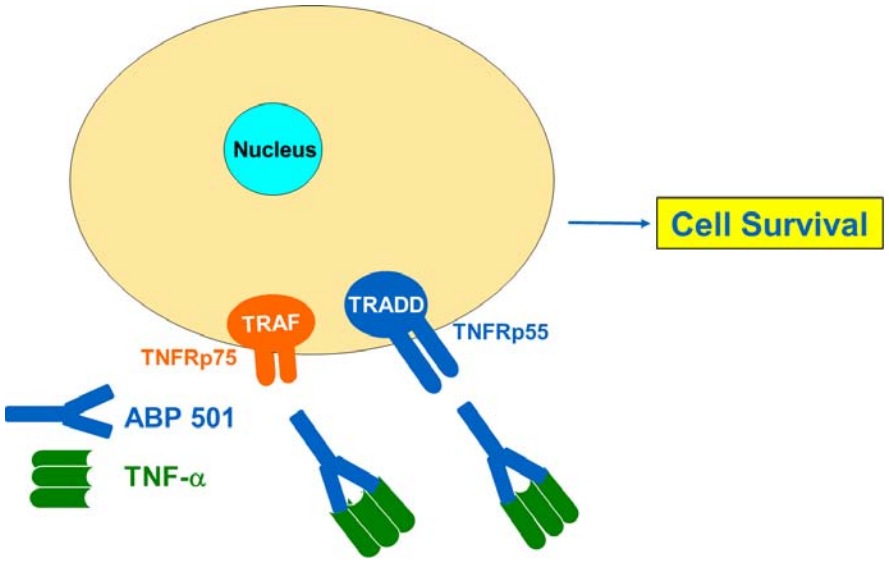
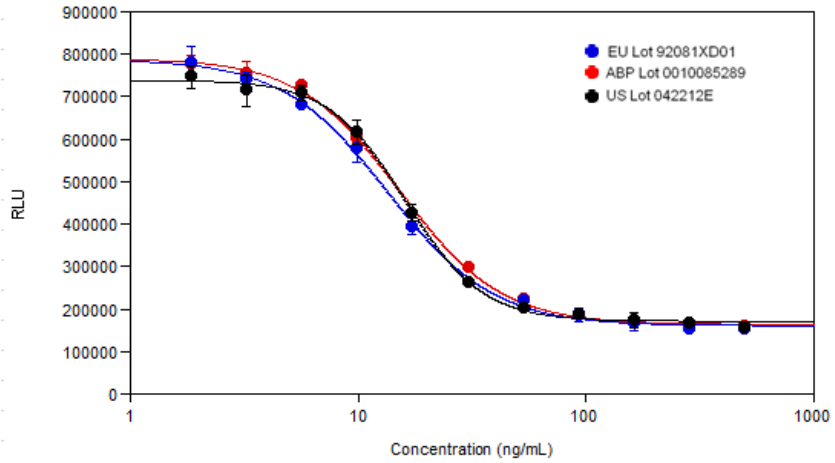


**Figure 78. Representative Plot of ABP 501, Adalimumab (US), and Adalimumab (EU) Dose-response in the Potency Assay**

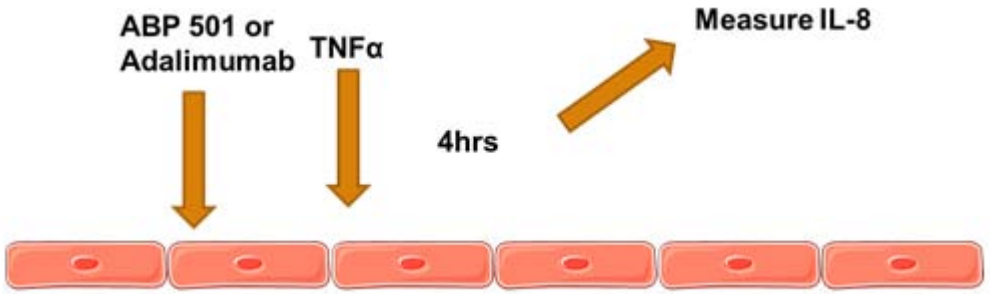



RLU = relative luminescence unit.
Overlay of nonconstrained dose-response curves. Each point is a mean of 3 within-assay replicates ± standard deviation.

## 10.6 Inhibition of Chemokine Production in Endothelial Cells

TNFα can induce inflammatory signaling, such as cytokine and chemokine induction, in human umbilical vein endothelial cells (HUVEC) in vitro. TNFα-induced IL-8 production in HUVEC is an NFκB-dependent response. An assay to monitor induced IL-8 secretion was developed as an orthogonal characterization assay, intended to compare similarity in inhibition of NFκB-dependent signaling pathways. As depicted in Figure 79, HUVEC were stimulated with 3 ng/mL human TNFα in the presence of increasing concentrations of ABP 501, adalimumab (US), or adalimumab (EU). The resulting IL-8 secretion was assessed after 4 hours, by Mesoscale Discovery (MSD) single-spot ELISA. The test sample data was fit to a sigmoidal dose-response, without constraint, to calculate the $EC_{50}$ (effective concentration at which an inhibition of 50% of the maximal inhibition is observed) of the samples.

**Figure 79. Schematic of the ABP 501 HUVEC Bioassay**




HUVEC = human umbilical vein endothelial cells; IL = interleukin; TNFα = tumor necrosis factor alpha.

## 10.7 Binding to FcγRIIIa (158V)

A competitive AlphaLISA® binding assay was developed to assess the binding of ABP 501 and adalimumab to FcγRIIIa (158V), using a biotinylated human IgG1 as a competitor to the test article. The AlphaLISA®assay contains 2 bead types, an acceptor

bead and a donor bead. When FcγRIIIa-glutathione-S transferase (GST) and the biotinylated human IgG1 bind together, they bring the acceptor and donor beads into close proximity. When laser light is applied and the 2 beads are in proximity to one another, light production (luminescence) occurs, which is measured in a plate reader. When ABP 501 or adalimumab are present at sufficient concentrations to compete for the binding of FcγRIIIa-GST to the biotinylated human IgG1, a dose-dependent decrease in luminescence is observed. A schematic of the FcγRIIIa (158V) binding assay is shown in Figure 80. A constrained curve fit model was applied to the data, and 4-parameter data analysis was used to determine the $EC_{50}$ (effective concentration at which an inhibition of 50% of the maximal inhibition is observed). The binding activity is calculated based on the $EC_{50}$, and is reported as a percent of the activity of the reference standard. Representative dose-response curves for ABP 501 and adalimumab are shown in Figure 81.

**Figure 80. Schematic of the ABP 501 FcγRIIIa (158V) Binding Assay**

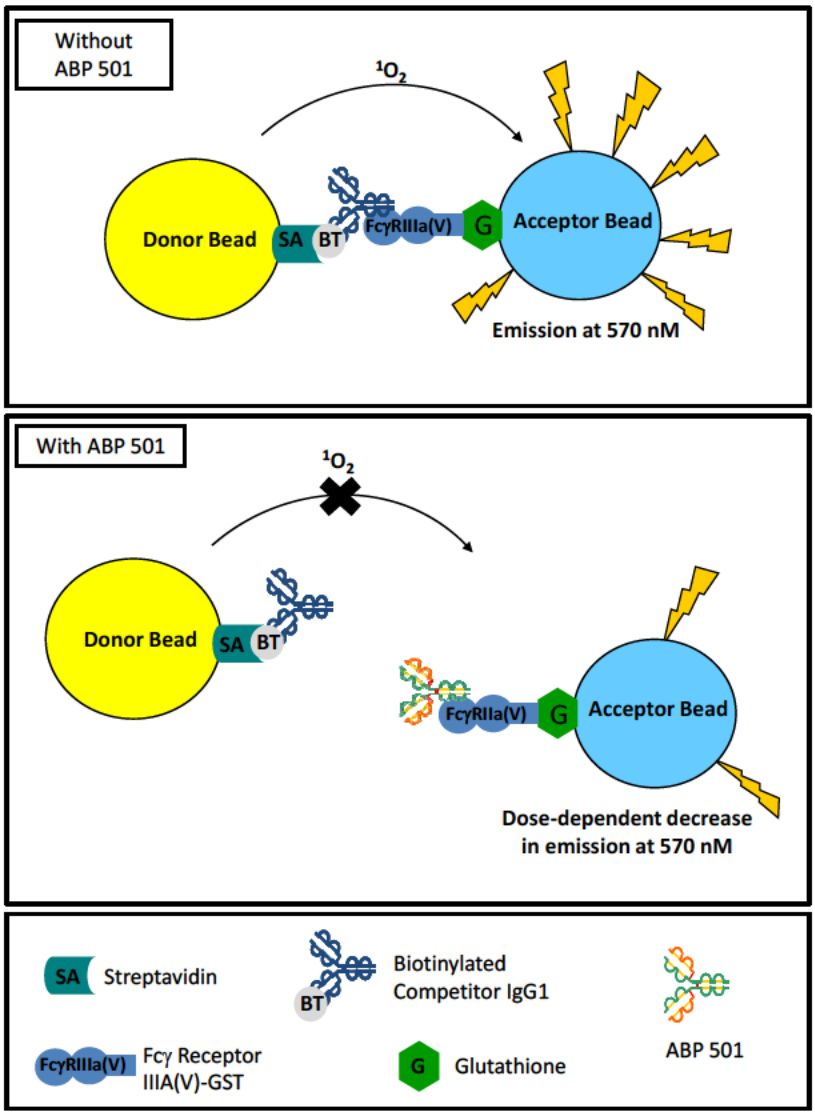
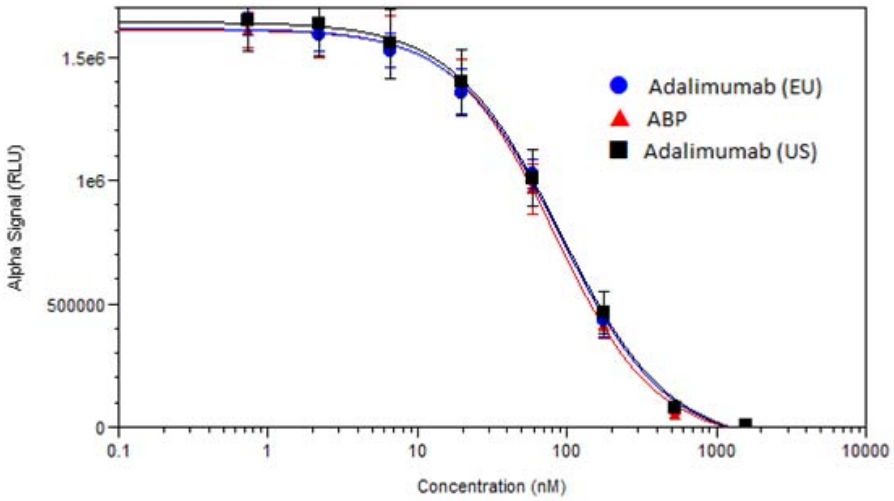


**Figure 81. Representative FcγRIIIa (158V) Binding by ABP 501, Adalimumab (US), and Adalimumab (EU)**




Each point is a mean of 3 within-assay replicates ± standard deviation

## 10.8 Antibody-dependent Cell-mediated Cytotoxicity (ADCC)

A sensitive assay has been developed to assess the ADCC activity of ABP 501 and adalimumab. A schematic of the ADCC assay is shown in Figure 82. In this assay, transmembrane TNFα-expressing CHO cells (Arora et al, 2009) are used as target cells. NK92-M1 cells, stably transfected with human FcγRIIIa (158V), are used as effector cells. Briefly, target cells are loaded with a fluorescent dye, calcein. Calcein-labeled target cells are opsonized with increasing concentrations of ABP 501 or adalimumab. NK92-M1 effector cells are then added. Upon target cell lysis, calcein is released into the media, and the fluorescence measured is proportional to the amount of ADCC activity. A constrained curve fit model was applied to the data, and 4-parameter data analysis was used to determine the $EC_{50}$ (effective concentration at which an inhibition of 50% of the maximal inhibition is observed). The binding activity is calculated based on the $EC_{50}$, and is reported as a percent of the activity of the reference standard. Representative dose-response curves for ABP 501 and adalimumab are shown in Figure 83.

**Figure 82. Schematic of the ABP 501 ADCC Assay**

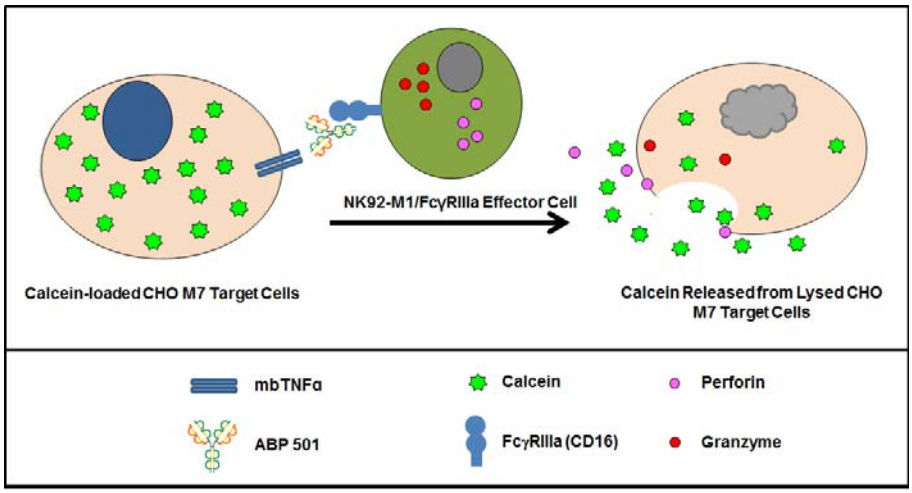
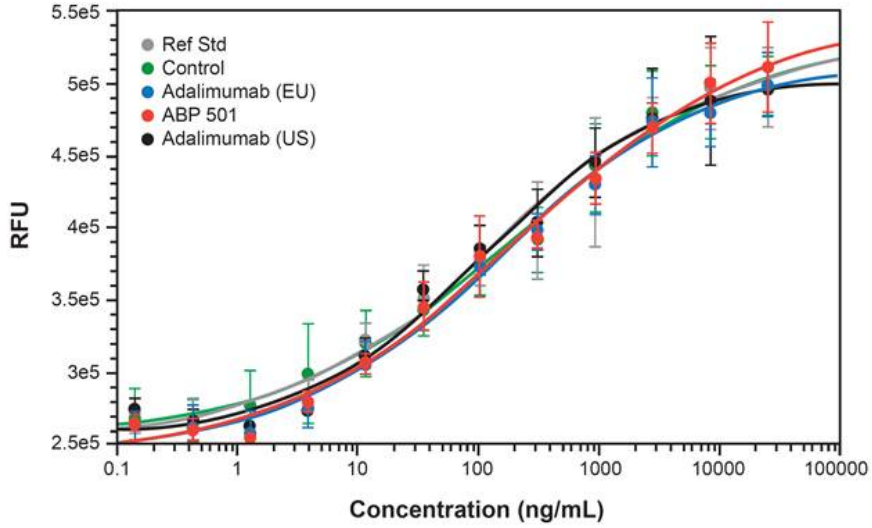


**Figure 83. Representative Antibody-dependent Cell-mediated Cytotoxicity Activity of ABP 501, Adalimumab (US), and Adalimumab (EU)**




Each point is the mean of 3 within-assay replicates ± standard deviation.

## 10.9 Complement-dependent Cytotoxicity (CDC)

In order to comparatively assess CDC activity, transmembrane TNFα-expressing CHO cells (Arora et al, 2009) are used as target cells. Target cells are loaded with a fluorescent dye, calcein. Calcein labeled target cells are opsonized with increasing concentrations of ABP 501 prior to co-incubation with human complement. Upon target cell lysis, calcein is released into the media, and the fluorescence measured is proportional to the amount of CDC activity. A schematic of the CDC assay is shown in Figure 84. A constrained curve fit model was applied to the data, and 4-parameter data analysis was used to determine the $EC_{50}$ (effective concentration at which an inhibition of 50% of the maximal inhibition is observed). The binding activity is calculated based on the $EC_{50}$, and is reported as a percent of the activity of the reference standard. Representative dose-response curves for ABP 501 and adalimumab are shown in Figure 85.

**Figure 84. Schematic of the ABP 501 CDC Assay**

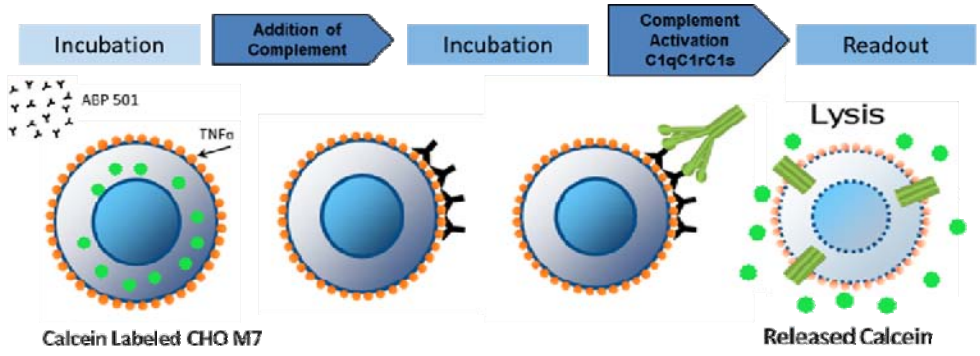
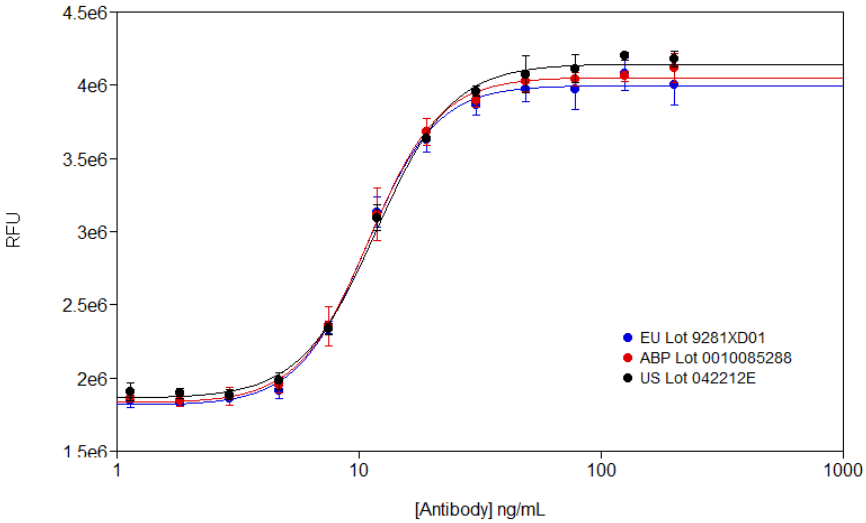


**Figure 85. Representative CDC Activity of ABP 501, Adalimumab (US), and Adalimumab (EU)**




Each point is the mean of 3 within-assay replicates ± standard deviation.

### 10.10 Binding to FcRn

A cell-based FcRn binding assay was developed to test the binding of the ABP 501 and adalimumab to FcRn. The assay is based on the ability of ABP 501 or adalimumab to compete with fluorescently labeled recombinant IgG1 for binding to cell surface-expressed FcRn. Thus, a reduction in cell bound fluorescence is observed with increasing concentrations of ABP 501 or adalimumab. A schematic of the cell-based FcRn binding assay is shown in Figure 86. A constrained curve fit model was applied to the data, and 4-parameter data analysis was used determine the $IC_{50}$ (effective concentration at which an inhibition of 50% of the maximal inhibition is observed). The binding activity is calculated based on the $IC_{50}$, and is reported as a percent of the activity of the reference standard. Representative dose-response curves for ABP 501 and adalimumab are shown in Figure 87.

**Figure 86. Schematic of the ABP 501 FcRn Binding Assay**

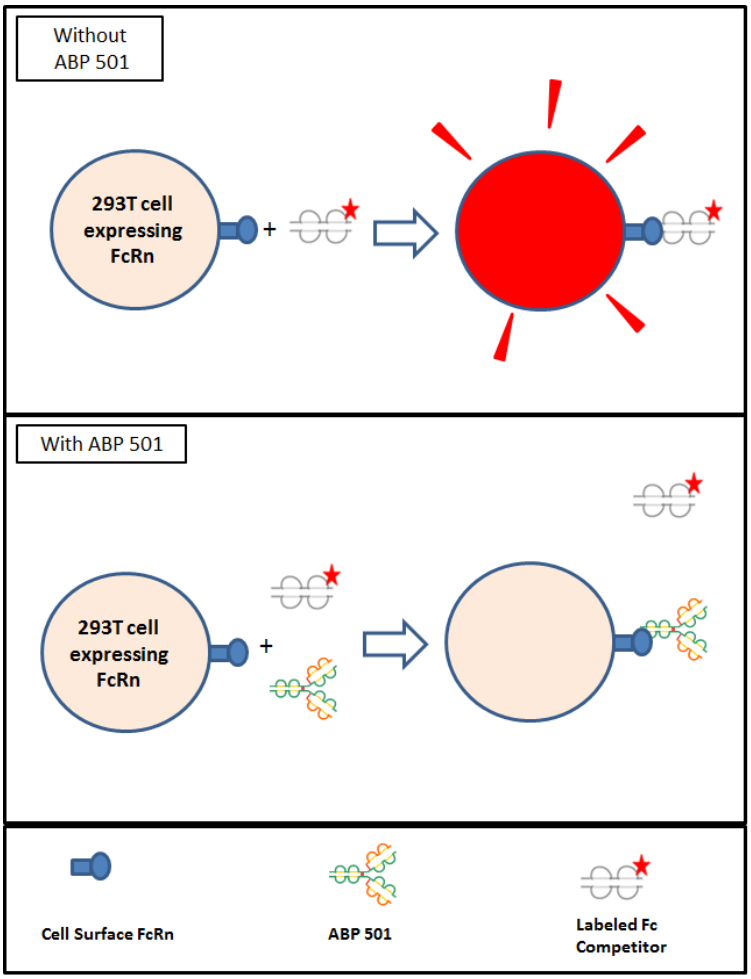
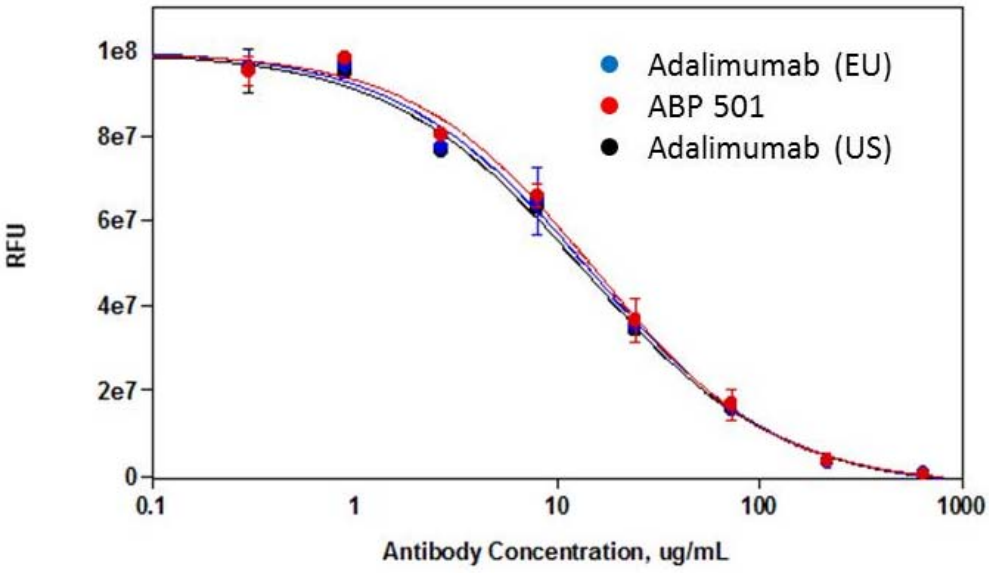



**Figure 87. Representative FcRn Binding of ABP 501, Adalimumab (US), and Adalimumab (EU)**




RFU = relative fluorescence unit.

## Appendix 2. Summary of Testing Strategy and Immunogenicity Methods

In alignment with current FDA guidance, Amgen implemented a tiered approach using immunoassay screening and confirmatory assays to detect binding antibodies to ABP 501 and adalimumab. If a sample tested positive for binding, then that sample was further tested for neutralizing antibodies. Amgen developed state-of-the-art methods to detect anti-drug antibodies that are tolerant of drug, rheumatoid factor, and soluble TNF$\alpha$ to assess the immunogenicity of ABP 501 and adalimumab.

An electrochemiluminescent bridging immunoassay was used for the detection of antibodies that are capable of binding to ABP 501 and adalimumab. Samples were diluted into a low pH buffer to disrupt drug-anti-drug antibody immune complexes, resulting in better drug tolerance. Drug conjugated to biotin and ruthenium in Tris buffer containing etanercept (which binds soluble TNF) was then added to the sample. If anti-drug antibodies are present in the sample, the anti-drug antibody will form a bridge between the biotin-drug and the ruthenylated drug. After a brief incubation, an aliquot of the neutralized sample was then added to a streptavidin high-bind plate (reduced binding to rheumatoid factor) to capture the anti-drug antibody-drug conjugate complex. The amount of anti-drug antibody present is proportional to the amount of electrochemiluminescence signal. Samples greater than the validated cut point were then tested in the presence of drug to confirm specificity of the response. The magnitude of a positive antibody response was reported as electrochemiluminescence of the sample (signal) relative to the electrochemiluminescence of the negative control or noise (signal to noise ratio) for each sample.

Amgen developed adalimumab-specific immunoassays for each of the 3 products (ABP 501, adalimumab [US], and adalimumab [EU]) using a common positive control antibody to provide additional assurance that product specific anti-drug antibodies that might form in a given subject was detected. In addition, all samples collected, irrespective of treatment, were analyzed in the ABP 501 assay and the adalimumab comparator assay(s). The immunological cross-reactivity of anti-drug antibody results was determined across the designated immunoassays to assess immunological reactivity by accessing the concordance in these assays.

By combining the highly sensitive detection technology (electrochemiluminescence) and sample pre-treatment with low pH, the assay provided sensitive detection of anti-drug antibody (< 25 ng/mL) in the presence of high drug levels (25 ng/mL anti-drug antibody in presence of 25 µg/mL drug). Compared to enzyme-linked immunosorbent assays,

which are historically less sensitive and drug tolerant in the detection of anti-adalimumab antibodies, the electrochemiluminescence method was more sensitive and drug tolerant.

The detection of neutralizing antibodies used either a cell-based assay (for the PK similarity study) or a target-binding assay (rheumatoid arthritis and plaque psoriasis studies). Both methods used ABP 501 for the detection of neutralizing antibodies.

A cell-based assay, validated to support the PK similarity study used a TNF-responding A549 cell line resulting in a TNF$\alpha$-induced phosphorylation of NF$\kappa$B. The phosphor-NF$\kappa$B in the cell lysate was measured by an electrochemiluminescent assay and is inversely proportional to the amount of neutralizing antibody presence in the sample. Despite good assay sensitivity and drug tolerance, this platform did not have appropriate throughput to handle routine titer analysis to support the multiple dose rheumatoid arthritis and plaque psoriasis studies. Thus a new competitive ligand-binding assay was validated.

The new method for the rheumatoid arthritis and plaque psoriasis studies used biotinylated soluble TNF$\alpha$, which forms a complex with ruthenylated drug. The complex was captured on a streptavidin plate and the electrochemiluminescent signal is inversely proportional to the amount of neutralizing antibody presence in a sample. Both a screening and confirmatory assay was run to confirm a neutralizing antibody. For positive neutralizing antibodies, the highest dilution that yields a positive result was reported as the titer.